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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4	Apr 09	ZDB will be removed from STN
NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 26	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 27	Oct 21	EVENTLINE has been reloaded
NEWS 28	Oct 24	BEILSTEIN adds new search fields
NEWS 29	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 30	Oct 25	MEDLINE SDI run of October 8, 2002
NEWS 31	Nov 18	DKILIT has been renamed APOLLIT
NEWS 32	Nov 25	More calculated properties added to REGISTRY
NEWS 33	Dec 02	TIBKAT will be removed from STN
NEWS 34	Dec 04	CSA files on STN
NEWS 35	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 36	Dec 17	TOXCENTER enhanced with additional content
NEWS 37	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 38	Dec 30	ISMEC no longer available
NEWS 39	Jan 13	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 40	Jan 21	NUTRACEUT offering one free connect hour in February 2003
NEWS 41	Jan 21	PHARMAML offering one free connect hour in February 2003
NEWS 42	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 43	Feb 13	CANCERLIT is no longer being updated

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NEWS 44   Feb 24  METADEX enhancements
NEWS 45   Feb 24  PCTGEN now available on STN
NEWS 46   Feb 24  TEMA now available on STN
NEWS 47   Feb 26  NTIS now allows simultaneous left and right truncation
NEWS 48   Feb 26  PCTFULL now contains images
NEWS 49   Mar 04  SDI PACKAGE for monthly delivery of multifile SDI results

NEWS EXPRESS  January 6 CURRENT WINDOWS VERSION IS V6.01a,
              CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
              AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
NEWS HOURS    STN Operating Hours Plus Help Desk Availability
NEWS INTER    General Internet Information
NEWS LOGIN    Welcome Banner and News Items
NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
NEWS WWW      CAS World Wide Web Site (general information)

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FILE 'HOME' ENTERED AT 09:24:40 ON 14 MAR 2003

=> FIL MEDLINE BIOSIS EMBASE CA SCISEARCH
COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                              ENTRY    SESSION
FULL ESTIMATED COST                            0.63       0.63

FILE 'MEDLINE' ENTERED AT 09:26:30 ON 14 MAR 2003

FILE 'BIOSIS' ENTERED AT 09:26:30 ON 14 MAR 2003
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FILE 'SCISEARCH' ENTERED AT 09:26:30 ON 14 MAR 2003
COPYRIGHT (C) 2003 Institute for Scientific Information (ISI) (R)

=> s (?nuclei? acid?) and (oligo? or antisense? or (complem? (2n) (nuclei? or
oligo?)))
   4 FILES SEARCHED...
L1        86292 (?NUCLEI? ACID?) AND (OLIGO? OR ANTISENSE? OR (COMPLEM? (2N)
                (NUCLEI? OR OLIGO?)))

=> s l1 and modif?
L2         9137 L1 AND MODIF?
```

```
=> s l2 and (resista? (2n) (nucle? or degrad?))
L3          305 L2 AND (RESISTA? (2N) (NUCLE? OR DEGRAD?))

=> s l3 and (2')
MISMATCHED QUOTE '(2')'
Quotation marks (or apostrophes) must be used in pairs,
one before and one after the expression you are setting
off or masking.

=> s l3 and (2 (5n) modif?)
L4           76 L3 AND (2 (5N) MODIF?)

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5           48 DUP REM L4 (28 DUPLICATES REMOVED)

=> d his

     (FILE 'HOME' ENTERED AT 09:24:40 ON 14 MAR 2003)

     FILE 'MEDLINE, BIOSIS, EMBASE, CA, SCISEARCH' ENTERED AT 09:26:30 ON 14
     MAR 2003
L1         86292 S (?NUCLEI? ACID?) AND (OLIGO? OR ANTISENSE? OR (COMPLEM? (2N)
L2          9137 S L1 AND MODIF?
L3           305 S L2 AND (RESISTA? (2N) (NUCLE? OR DEGRAD?))
L4            76 S L3 AND (2 (5N) MODIF?)
L5            48 DUP REM L4 (28 DUPLICATES REMOVED)

=> s l1 (2n) l2
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L1 (2A) L7'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L2 (2A) L8'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L3 (2A) L9'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L4 (2A) L10'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L5 (2A) L11'
L6         9137 L1 (2N) L2

=> s (oligo? or antisense? or (complem? (2n) (nuclei? or oligo?))) (3n) modif?
L7        13231 (OLIGO? OR ANTISENSE? OR (COMPLEM? (2N) (NUCLEI? OR OLIGO?)))
                (3N) MODIF?

=> s l7 and (resista? (2n) (nucle? or degrad?))
L8           539 L7 AND (RESISTA? (2N) (NUCLE? OR DEGRAD?))

=> d his

     (FILE 'HOME' ENTERED AT 09:24:40 ON 14 MAR 2003)

     FILE 'MEDLINE, BIOSIS, EMBASE, CA, SCISEARCH' ENTERED AT 09:26:30 ON 14
     MAR 2003
L1         86292 S (?NUCLEI? ACID?) AND (OLIGO? OR ANTISENSE? OR (COMPLEM? (2N)
L2          9137 S L1 AND MODIF?
L3           305 S L2 AND (RESISTA? (2N) (NUCLE? OR DEGRAD?))
L4            76 S L3 AND (2 (5N) MODIF?)
L5            48 DUP REM L4 (28 DUPLICATES REMOVED)
L6          9137 S L1 (2N) L2
L7         13231 S (OLIGO? OR ANTISENSE? OR (COMPLEM? (2N) (NUCLEI? OR OLIGO?)))
L8           539 S L7 AND (RESISTA? (2N) (NUCLE? OR DEGRAD?))
```

```
=> s l8 and (2 (5n) modif?)
L9          156 L8 AND (2 (5N) MODIF?)

=> s l9 and (halo? or fluoro? or iodo? or bromo? or azid? or amino? or alkox? or
alkyl? or thio?)
   4 FILES SEARCHED...
L10          76 L9 AND (HALO? OR FLUORO? OR IODO? OR BROMO? OR AZID? OR AMINO?
                OR ALKOX? OR ALKYL? OR THIO?)

=> d his

     (FILE 'HOME' ENTERED AT 09:24:40 ON 14 MAR 2003)

     FILE 'MEDLINE, BIOSIS, EMBASE, CA, SCISEARCH' ENTERED AT 09:26:30 ON 14
     MAR 2003
L1         86292 S (?NUCLEI? ACID?) AND (OLIGO? OR ANTISENSE? OR (COMPLEM? (2N)
L2          9137 S L1 AND MODIF?
L3           305 S L2 AND (RESISTA? (2N) (NUCLE? OR DEGRAD?))
L4            76 S L3 AND (2 (5N) MODIF?)
L5            48 DUP REM L4 (28 DUPLICATES REMOVED)
L6          9137 S L1 (2N) L2
L7         13231 S (OLIGO? OR ANTISENSE? OR (COMPLEM? (2N) (NUCLEI? OR OLIGO?)))
L8           539 S L7 AND (RESISTA? (2N) (NUCLE? OR DEGRAD?))
L9           156 S L8 AND (2 (5N) MODIF?)
L10           76 S L9 AND (HALO? OR FLUORO? OR IODO? OR BROMO? OR AZID? OR AMIN

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11           47 DUP REM L10 (29 DUPLICATES REMOVED)

=> s l10 and ((mix? or diff? or ((two or 2) or more)) (w) modif?)
   2 FILES SEARCHED...
   3 FILES SEARCHED...
L12           12 L10 AND ((MIX? OR DIFF? OR ((TWO OR 2) OR MORE)) (W) MODIF?)

=> d l12 1-12 ibib abs

L12  ANSWER 1 OF 12  BIOSIS  COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER:    2000:324544  BIOSIS
DOCUMENT NUMBER:     PREV200000324544
TITLE:               Zwitterionic oligonucleotides with 2'-O-(3-(N,N-
                     dimethylamino)propyl)-RNA modification: Synthesis and
                     properties.
AUTHOR(S):           Prakash, Thazha P.; Manoharan, Muthiah (1); Fraser,
                     Allister S.; Kawasaki, Andrew M.; Lesnik, Elena A.; Owens,
                     Stephen R.
CORPORATE SOURCE:    (1) Department of Medicinal Chemistry, Isis
                     Pharmaceuticals, 2292 Faraday Ave, Carlsbad, CA, 92008 USA
SOURCE:              Tetrahedron Letters, (19 June, 2000) Vol. 41, No. 25, pp.
                     4855-4859. print.
                     ISSN: 0040-4039.
DOCUMENT TYPE:       Article
LANGUAGE:            English
SUMMARY LANGUAGE:    English
AB   A novel 2'-modification, 2
     '-O-(3-(N,N-dimethylamino)propyl) or 2'-O-DMAP, has been incorporated into
     oligonucleotides and compared to the known 2'-O-(3-aminopropyl)
     or 2'-O-AP modification for antisense
     properties. The 2'-O-DMAP modified
     oligonucleotides exhibit very high nuclease
     resistance like the 2'-O-AP modification due
```

to the 'charge effect' and maintain high binding affinity to target RNA relative to known **modifications** when a few **2'-O-DMAP** residues are dispersed throughout the oligonucleotide.

L12 ANSWER 2 OF 12 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000234553 EMBASE
TITLE: Zwitterionic oligonucleotides with 2'-O-[3-(N,N-dimethylamino)propyl]- RNA modification: Synthesis and properties.
AUTHOR: Prakash T.P.; Manoharan M.; Fraser A.S.; Kawasaki A.M.; Lesnik E.A.; Owens S.R.
CORPORATE SOURCE: M. Manoharan, Department of Medicinal Chemistry, Isis Pharmaceuticals, 2292 Faraday Ave, Carlsbad, CA 92008, United States. mmanoharan@isisph.com
SOURCE: Tetrahedron Letters, (19 Jun 2000) 41/25 (4855-4859). Refs: 20
ISSN: 0040-4039 CODEN: TELEAY
PUBLISHER IDENT.: S 0040-4039(00)00703-6
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A novel **2'-modification, 2'-O-[3-(N,N-dimethylamino)propyl]** or 2'-O- DMAP, has been incorporated into oligonucleotides and compared to the known 2'-O-(3-**aminopropyl**) or **2'-O-AP modification** for **antisense** properties. The **2'-O-DMAP modified oligonucleotides** exhibit very high **nuclease resistance** like the **2'-O-AP modification** due to the 'charge effect' and maintain high binding affinity to target RNA relative to known **modifications** when a few **2'-** O-DMAP residues are dispersed throughout the oligonucleotide. (C) 2000 Elsevier Science Ltd.

L12 ANSWER 3 OF 12 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 137:365293 CA
TITLE: **2'-O-[2-(Methylthio)ethyl]-Modified Oligonucleotide**: An Analogue of **2'-O-[2-(Methoxy)-ethyl]-Modified Oligonucleotide** with Improved Protein Binding Properties and High Binding Affinity to Target RNA
AUTHOR(S): Prakash, Thazha P.; Manoharan, Muthiah; Kawasaki, Andrew M.; Fraser, Allister S.; Lesnik, Elena A.; Sioufi, Namir; Leeds, Janet M.; Teplova, Marianna; Egli, Martin
CORPORATE SOURCE: Department of Medicinal Chemistry, Isis Pharmaceuticals, Carlsbad, CA, 92008, USA
SOURCE: Biochemistry (2002), 41(39), 11642-11648
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A novel **2'-modification, 2'-O-[2-(methylthio)ethyl]** or 2'-O-MTE, has been incorporated into oligonucleotides and evaluated for properties relevant to antisense activity. The results were compared with the previously characterized 2'-O-[2-(methoxy)ethyl] **2'-O-MOE modification**. As expected, the **2'-O-MTE modified oligonucleotides** exhibited improved binding to human serum albumin compared to the **2'-O-MOE modified**

oligonucleotides. The 2'-O-MTE oligonucleotides maintained high binding affinity to target RNA. Nuclease digestion of 2'-O-MTE oligonucleotides showed that they have limited **resistance** to exonuclease **degrdn**. We analyzed the crystal structure of a decamer DNA duplex contg. the **2'-O-MTE modification**. Anal. of the crystal structure provides insight into the improved RNA binding affinity, protein binding affinity and limited resistance of **2'-O-MTE modified oligonucleotides** to exonuclease degrdn.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 12 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 137:63428 CA
TITLE: Preparation, **nuclease resistance**, and protein binding of **oligonucleotide** analogs having **modified** dimers
INVENTOR(S): Cook, Phillip Dan; Manoharan, Muthiah; Bhat, Balkrishen
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: U.S., 33 pp., Cont.-in-part of U. S. Ser. No. 248,386. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 100
PATENT INFORMATION:

Could have 2 diff. subst. @ X - not shown have to - doesn't teach from Appl. Markush group

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6420549	B1	20020716	US 1998-131102	19980807
US 5859221	A	19990112	US 1995-468037	19950606
US 5965722	A	19991012	US 1997-848840	19970430
AU 713740	B2	19991209	AU 1997-26244	19970624
AU 9726244	A1	19971106		
US 6232463	B1	20010515	US 1998-128508	19980804
US 6359124	B1	20020319	US 1999-248386	19990212
WO 2000008214	A1	20000217	WO 1999-US18023	19990806
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9953448	A1	20000228	AU 1999-53448	19990806

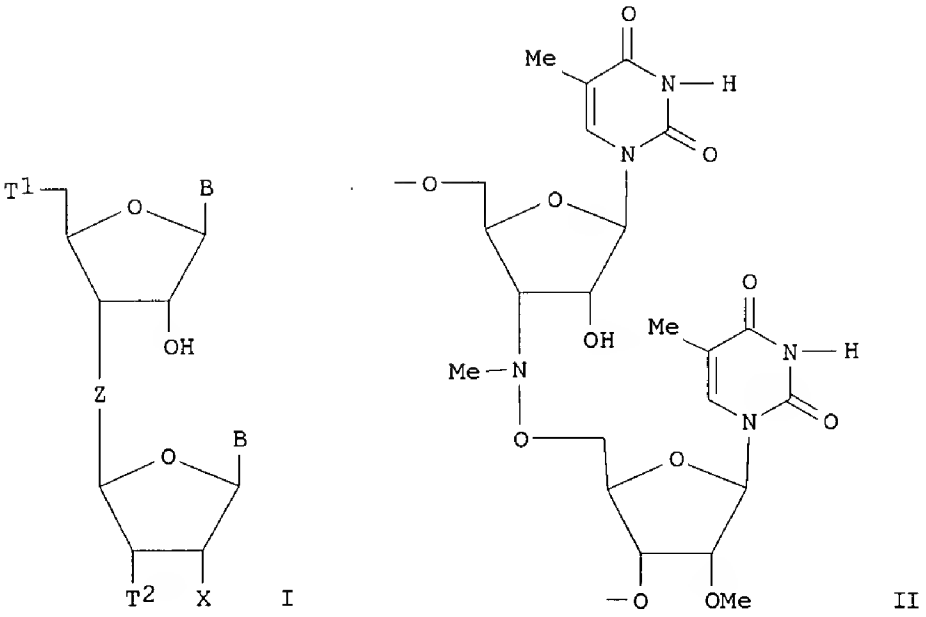
PRIORITY APPLN. INFO.:

US 1995-468037	A2	19950606
US 1997-848840	A3	19970430
US 1999-248386	A2	19990212
US 1990-463358	B2	19900111
US 1990-566977	B2	19900813
US 1991-801168	B1	19911120
US 1991-814961	B2	19911224
US 1992-835932	A2	19920305
US 1992-854634	B2	19920701
US 1992-958134	B2	19921005
WO 1992-US11339	B1	19921223
US 1993-7996	B2	19930121
AU 1993-38025	A3	19930225
US 1993-39979	B1	19930330
US 1993-40526	A2	19930331

US 1993-40903	A3	19930331
US 1993-40933	B1	19930331
WO 1993-US9346	B1	19931001
US 1994-227180	A2	19940413
US 1994-244993	A2	19940621
US 1994-300072	A3	19940902
US 1994-317289	A2	19941003
US 1994-335046	A2	19941107
US 1995-411734	A2	19950403
US 1995-465866	A2	19950606
US 1995-488256	A2	19950607
US 1997-794493	A2	19970204
US 1997-948151	A1	19971009
US 1998-131102	A	19980807
WO 1999-US18023	W	19990806

OTHER SOURCE(S): MARPAT 137:63428

GI



AB Modified dimers having a ribose sugar moiety in the 5'-nucleoside and a **2'-modified** sugar in the 3'-nucleoside I wherein Z is a covalent inter-sugar linkage; each T1 and T2 are independently, OH, OR, CH2R, NHR, SH, SR, or a blocked hydroxyl; B is a heterocyclic base; X is F, OR, SR or -NRR2; R is **alkyl**, or a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur and wherein said ring system is aliph., unsatd. aliph., arom. or heterocyclic; and wherein any available hydrogen atom of said ring system is each replaceable with an **alkoxy**, **alkylamino**, urea or **alkylurea** group; are provided. The modified dimers are useful in the prepn. of oligonucleotide analogs having enhanced properties compared to native oligonucleotides, including increased **nuclease resistance**, enhanced binding affinity and improved protein binding. Thus, GTCGTACC-II-TCCGGTCC was prepd. and tested for its serum and cytoplasmic **nuclease resistance** (no data).

REFERENCE COUNT: 161 THERE ARE 161 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 12 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 133:222959 CA
TITLE: Zwitterionic oligonucleotides with 2'-O-[3-(N,N-dimethylamino)propyl]-RNA modification: synthesis and properties
AUTHOR(S): Prakash, T. P.; Manoharan, M.; Fraser, A. S.; Kawasaki, A. M.; Lesnik, E. A.; Owens, S. R.
CORPORATE SOURCE: Department of Medicinal Chemistry, Isis Pharmaceuticals, Carlsbad, CA, 92008, USA
SOURCE: Tetrahedron Letters (2000), 41(25), 4855-4859
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A novel **2'-modification, 2**'-O-[3-(N,N-dimethylamino)propyl] or 2'-O-DMAP, has been incorporated into oligonucleotides and compared to the known 2'-O-(3-**aminopropyl**) or **2'**-O-AP **modification** for **antisense** properties. The **2'**-O-DMAP **modified** **oligonucleotides** exhibit very high **nuclease** **resistance** like the **2'**-O-AP **modification** due to the 'charge effect' and maintain high binding affinity to target RNA relative to known **modifications** when a few **2'**-O-DMAP residues are dispersed throughout the oligonucleotide.

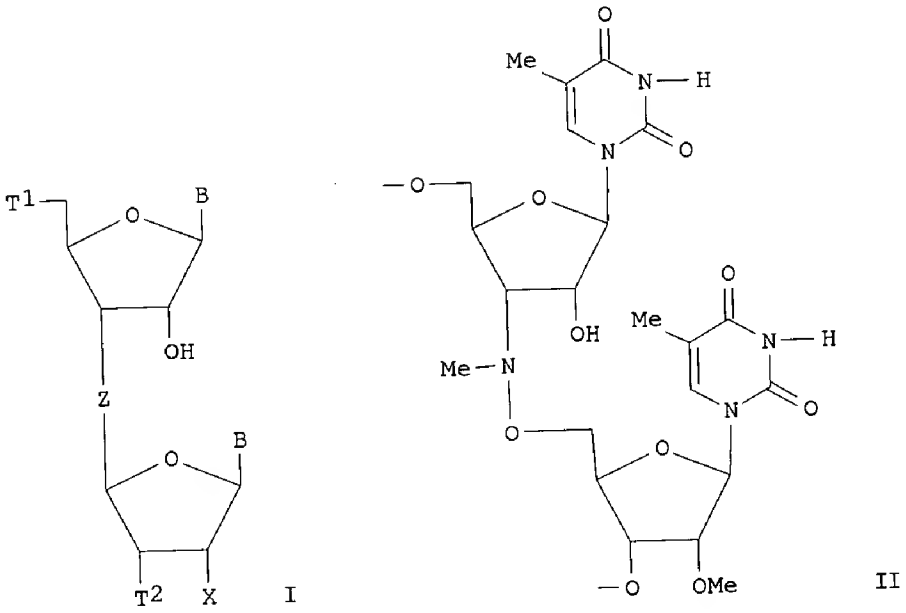
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 6 OF 12 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 132:152089 CA
TITLE: Preparation, **nuclease resistance,** and protein binding of **oligonucleotide** analogs having **modified** dimers
INVENTOR(S): Cook, Phillip Dan; Manoharan, Muthiah; Bhat, Balkrishen
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 100
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000008214	A1	20000217	WO 1999-US18023	19990806
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 713740	B2	19991209	AU 1997-26244	19970624
AU 9726244	A1	19971106		
US 6232463	B1	20010515	US 1998-128508	19980804
US 6420549	B1	20020716	US 1998-131102	19980807

AU 9953448 A1 20000228 AU 1999-53448 19990806
PRIORITY APPLN. INFO.: US 1998-131102 A 19980807
AU 1993-38025 A3 19930225
US 1995-468037 A2 19950606
US 1997-848840 A3 19970430
US 1997-948151 A1 19971009
US 1999-248386 A2 19990212
WO 1999-US18023 W 19990806

OTHER SOURCE(S): MARPAT 132:152089
GI



AB Modified dimers having a ribose sugar moiety in the 5'-nucleoside and a **2'-modified** sugar in the 3'-nucleoside I wherein Z is a covalent inter-sugar linkage; each T1 and T2 is, independently, OH, OR1, CH2R1, NHR1, SH, SR1, or a blocked hydroxyl; R1 is **alkyl**; Bx is a heterocyclic base; X is F, OR, SR or -NRR2; R is **alkyl**, or a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur and wherein said ring system is aliph., unsatd. aliph., arom. or heterocyclic; and wherein any available hydrogen atom of said ring system is each replaceable with an **alkoxy**, **alkylamino**, urea or **alkylurea** group; are provided. The modified dimers are useful in the prepn. of oligonucleotide analogs having enhanced properties compared to native oligonucleotides, including increased **nuclease resistance**, enhanced binding affinity and improved protein binding. Thus, GTCGTACC-II-TCCGGTCC was prepd. and tested for its serum and cytoplasmic **nuclease resistance** (no data).

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 12 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 131:237986 CA
TITLE: Gapped 2'-**alkyl** or 2-deoxy-erythro-pentofuranosyl or other **2'-modified**

oligonucleotides for **antisense** therapy
INVENTOR(S): Cook, Phillip Dan; Monia, Brett P.
PATENT ASSIGNEE(S): Isis Pharmaceuticals Inc., USA
SOURCE: U.S., 34 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 100
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5955589	A	19990921	US 1995-465880	19950606
AU 713740	B2	19991209	AU 1997-26244	19970624
AU 9726244	A1	19971106		
US 6232463	B1	20010515	US 1998-128508	19980804
US 6399754	B1	20020604	US 1998-135202	19980817

PRIORITY APPLN. INFO.: US 1991-814961 B2 19911224
WO 1992-US11339 B2 19921223
AU 1993-38025 A3 19930225
US 1994-244993 A2 19940621
US 1995-465880 A2 19950606
US 1995-471973 A3 19950606
US 1997-948151 A1 19971009

AB Oligonucleotides and other macromols. are provided which have increased **nuclease resistance**, substituent groups for increasing binding affinity to complementary strand, and subsequences of 2'-deoxy-erythro-pentofuranosyl nucleotides that activate RNase H. Such oligonucleotides and macromols. are useful for diagnostics and other research purposes, for modulating the expression of a protein in organisms, and for the diagnosis, detection and treatment of other conditions susceptible to oligonucleotide therapeutics. For the purpose of illustration, the antisense oligonucleotides of the invention are used in a H-ras-luciferase expression system, to hybridize with nucleic acids related to protein kinase C-.alpha., to inhibit c-raf expression, and as antiviral agents.

REFERENCE COUNT: 117 THERE ARE 117 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 8 OF 12 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 124:283703 CA
TITLE: Conjugates of metal complexes and oligoribonucleotides which bind specifically to selected target structures for MRI
INVENTOR(S): Platzek, Johannes; Niedballa, Ulrich; Raduechel, Bernd; Muehler, Andreas; Speck, Ulrich
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger. Offen., 19 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4424923	A1	19960118	DE 1994-4424923	19940714
WO 9602669	A1	19960201	WO 1995-EP2686	19950712

W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NO, NZ, PL, PT, RO, RU,

SD, SE, SK, UA, US, UZ, VN
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

AU 9531090	A1	19960216	AU 1995-31090	19950712
EP 770146	A1	19970502	EP 1995-926850	19950712
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10511842	T2	19981117	JP 1995-504000	19950712
ZA 9505894	A	19960730	ZA 1995-5894	19950714
PRIORITY APPLN. INFO.:			DE 1994-4424923	19940714
			DE 1994-4445076	19941205
			WO 1995-EP2686	19950712

teaches 2'O- not explicitly that 2 be on same molecule

AB Conjugates of **modified oligonucleotides** with metal complexes or complexing agents, which bind specifically to biol. target structures, are useful in diagnostic NMR imaging. The **oligonucleotides** are **modified** to render them **resistant** to **degrdn**. by endogenous nucleases, e.g. by O-**alkylation**, **halogenation**, amination, or redn. at the 2' position or by replacement of phosphodiester groups by phosphorothioate, phosphorodithioate, or **alkylphosphonate** linkages. The oligonucleotides are selected from a random mixt. for binding to a target such as a non-nucleic acid macromol., tissue, or organ. Thus, a 30-mer oligonucleotide ligand for serine proteinase was conjugated with the linker .beta.-cyanoethyl S-trityl-6-mercaptohexyl N,N-diisopropylphosphoramidite, then with 1,4,7,10-tetraaza-2-[(5-aza-8-maleimido-6-oxo)octyl]cyclododecane-1,4,7,10-tetraacetic acid, and complexed with Gd3+ for use in NMR imaging.

L12 ANSWER 9 OF 12 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 124:254781 CA
TITLE: Conjugates of metal complexes and oligoribonucleotides which bind specifically to selected target structures
INVENTOR(S): Dinkelborg, Ludger; Hilger, Christoph-Stephan; Niedballa, Ulrich; Platzek, Johannes; Raduechel, Bernd; Speck, Ulrich
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger. Offen., 25 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4424922	A1	19960118	DE 1994-4424922	19940714
US 2002077306	A1	20020620	US 1995-488290	19950607
IL 114237	A1	20000831	IL 1995-114237	19950620
CA 2194558	AA	19960201	CA 1995-2194558	19950630
WO 9602274	A1	19960201	WO 1995-EP2539	19950630
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9529791	A1	19960216	AU 1995-29791	19950630
EP 777498	A1	19970611	EP 1995-925792	19950630
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1152879	A	19970625	CN 1995-194000	19950630
HU 76329	A2	19970828	HU 1997-100	19950630
JP 10503182	T2	19980324	JP 1995-504630	19950630
RU 2165771	C2	20010427	RU 1997-102039	19950630
ZA 9505895	A	19960219	ZA 1995-5895	19950714
NO 9700141	A	19970314	NO 1997-141	19970113
AU 9920360	A1	19990617	AU 1999-20360	19990312

AU 721330 B2 20000629

PRIORITY APPLN. INFO.:

DE 1994-4424922	A	19940714
US 1994-336127	B2	19941104
US 1994-336128	B2	19941104
DE 1994-4445078	A	19941205
US 1994-357573	B2	19941215
US 1994-358065	B2	19941215
US 1995-409813	B1	19950324
AU 1995-29791	A3	19950630
WO 1995-EP2539	W	19950630

AB Conjugates of **modified oligonucleotides** with complexes of radioactive or stable metal isotopes, which bind specifically to biol. target structures, are useful in diagnostic imaging and radiotherapy. The **oligonucleotides** are **modified** to render them **resistant** to **degrdn.** by endogenous nucleases, e.g. by O-**alkylation, halogenation,** amination, or redn. at the 2' position or by replacement of phosphodiester groups by phosphorothioate, phosphorodithioate, or **alkylphosphonate** linkages. The oligonucleotides are selected from a random mixt. for binding to a target such as a non-nucleic acid macromol., tissue, or organ. Thus, a 30-mer oligonucleotide ligand for NGF was conjugated with the linker .beta.-cyanoethyl N,N-diisopropylamino-6-(trifluoroacetamido)-1-hexylphosphoramidite, then with 10-[7-(4-isothiocyanatophenyl)-2-hydroxy-5-oxo-7-(carboxymethyl)-4-azaheptyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (prepn. given), and complexed with 111In(III) for use as a radiodiagnostic agent.

L12 ANSWER 10 OF 12 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 115:232781 CA

TITLE: Preparation of **2'-modified nuclease-resistant oligonucleotide**

INVENTOR(S): Buhr, Chris A.; Matteucci, Mark

PATENT ASSIGNEE(S): Gilead Sciences, Inc., USA

SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9106556	A1	19910516	WO 1990-US6090	19901024
W: AU, CA, JP, KR				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
CA 2071510	AA	19910425	CA 1990-2071510	19901024
AU 9067157	A1	19910531	AU 1990-67157	19901024
AU 658562	B2	19950427		
EP 497875	A1	19920812	EP 1990-916605	19901024
EP 497875	B1	20000322		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 05504552	T2	19930715	JP 1990-515636	19901024
EP 942000	A2	19990915	EP 1999-107747	19901024
EP 942000	A3	20000315		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AT 190981	E	20000415	AT 1990-916605	19901024
US 5466786	A	19951114	US 1994-240508	19940510
US 5466786	B1	19980407		
US 5792847	A	19980811	US 1995-467422	19950606
US 6476205	B1	20021105	US 1998-131647	19980810
US 2003036649	A1	20030220	US 2002-186058	20020627

PRIORITY APPLN. INFO.:

US 1989-425857	A	19891024
EP 1990-916605	A3	19901024
WO 1990-US6090	A	19901024
US 1994-240508	A1	19940510
US 1995-467422	A1	19950606
US 1998-131647	A1	19980810

OTHER SOURCE(S): MARPAT 115:232781
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB **2'-Modified oligonucleotide** I [B = purine or pyridimidine residue; R3,R4 = H, PO3-2, protecting group, hydroxyl linking group; n = 1-220; Z = linking group, e.g., P(O)O, P(O)S, P(O)NR, etc.; R = H, C16 **alkyl**; A = H, (protected) OH, XY; X = O, S, NR, CRR; Y = linker, drug residue, e.g., netropsin, anthramycin, C2-6 **alkyl**, (substituted) C6-20 aryl] were prepd. via oligomerization of monomers II [R3 = H, (PO3)m, protecting group, hydroxyl linking group; m = 1-3; all others defined above]. The oligomers are **nuclease-resistant** and useful as nucleic acid hybridization probes (no data). Thus, 2'-N-acetylamino-3',5'-O-diacetyluridine was deacylated by KCN and treated with 4,4'-dimethoxytrityl chloride to give 2'-N-acetylamino-5'-O-(4,4'-dimethoxytrityl)uridine which was added to a mixt. of 1,2,4-triazole, 4-methylmorpholine, and PCl3 in CH2Cl. The mixt. formed was poured into 1M aq. Et3NH+HCO3- to give monomer III. This can be converted to title oligomers by known methods. Title dimers are said to be **resistant** to **nuclease** from snake venom for >140 min.

L12 ANSWER 11 OF 12 SCISEARCH COPYRIGHT 2003 ISI (R)

ACCESSION NUMBER:	2000:492353 SCISEARCH
THE GENUINE ARTICLE:	327LA
TITLE:	Zwitterionic oligonucleotides with 2'-O-[3-(N,N-dimethylamino)propyl]-RNA modification: synthesis and properties
AUTHOR:	Prakash T P; Manoharan M (Reprint); Fraser A S; Kawasaki A M; Lesnik E A; Owens S R
CORPORATE SOURCE:	ISIS PHARMACEUT, DEPT MED CHEM, 2292 FARADAY AVE, CARLSBAD, CA 92008 (Reprint); ISIS PHARMACEUT, DEPT MED CHEM, CARLSBAD, CA 92008
COUNTRY OF AUTHOR:	USA
SOURCE:	TETRAHEDRON LETTERS, (19 JUN 2000) Vol. 41, No. 25, pp. 4855-4859. Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND. ISSN: 0040-4039.
DOCUMENT TYPE:	Article; Journal
FILE SEGMENT:	PHYS; LIFE
LANGUAGE:	English
REFERENCE COUNT:	19

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A novel **2'-modification, 2'-O-[3-(N,N-dimethylamino)propyl]** or 2'-O-DMAP, has been incorporated into oligonucleotides and compared to the known 2'-O-(3-**aminopropyl**) or **2'-O-AP modification** for **antisense** properties. The **2'-O-DMAP modified oligonucleotides** exhibit very high **nuclease resistance** like the **2'-O-AP modification** due to the 'charge effect' and maintain high binding affinity to target RNA

relative to known **modifications** when a few **2'**-O-DMAP residues are dispersed throughout the oligonucleotide. (C) 2000 Elsevier Science Ltd. All rights reserved.

L12 ANSWER 12 OF 12 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 1999:403172 SCISEARCH
THE GENUINE ARTICLE: 197WC
TITLE: Inhibition of translation of hepatitis C virus RNA by **2'-modified antisense oligonucleotides**
AUTHOR: BrownDriver V (Reprint); Eto T; Lesnik E; Anderson K P; Hanecak R C
CORPORATE SOURCE: ISIS PHARMACEUT, 2280 FARADAY AVE, CARLSBAD, CA 92008 (Reprint); CHEMOSEROTHERAPEUT RES INST, KUMAMOTO 86912, JAPAN
COUNTRY OF AUTHOR: USA; JAPAN
SOURCE: ANTISENSE & NUCLEIC ACID DRUG DEVELOPMENT, (APR 1999) Vol. 9, No. 2, pp. 145-154.
Publisher: MARY ANN LIEBERT INC PUBL, 2 MADISON AVENUE, LARCHMONT, NY 10538.
ISSN: 1087-2906.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 50

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Inhibition of hepatitis C virus (HCV) gene expression by antisense oligonucleotides was investigated using both a rabbit reticulocyte lysate in vitro translation assay and a transformed human hepatocyte cell expression assay. Screening of overlapping oligonuceeotides complementary to the HCV 5' noncoding region and the core open reading frame (ORF) identified a region susceptible to translation inhibition between nucleotides 335 and 379, Comparison of 2'-deoxy-, 2'-O-methyl-, 2'-O-methoxyethyl-, **2'**-O-propyl-, and **2'-fluoro-modified** phosphodiester **oligoribonucleotides** demonstrated that increased translation inhibition correlated with both increased binding affinity and nuclease stability, In cell culture assays, **2'**-O-methoxyethyl-**modified oligonucleotides** inhibited HCV core protein synthesis with comparable potency to phosphorothioate oligodeoxynucleotides. Inhibition of HCV core protein expression by **2'-modified oligonucleotides** occurred by an RNase H-independent translational arrest mechanism.

=> s l5 or l11
L13 76 L5 OR L11

=> dup rem l13
PROCESSING COMPLETED FOR L13
L14 67 DUP REM L13 (9 DUPLICATES REMOVED)

=> d l14 1-67 ibib abs

L14 ANSWER 1 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:282976 BIOSIS
DOCUMENT NUMBER: PREV200200282976
TITLE: **Oligonucleotides** having A-DNA form and B-DNA form conformational geometry.
AUTHOR(S): Manoharan, Muthiah; Mohan, Venkatraman
ASSIGNEE: ISIS Pharmaceuticals, Inc.
PATENT INFORMATION: US 6369209 April 09, 2002
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Apr. 9, 2002) Vol. 1257, No. 2, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB **Modified oligonucleotides** containing both A-form conformation geometry and B-from conformation geometry nucleotides are disclosed. The B-form geometry allows the **oligonucleotide** to serve as substrates for RNase H when bound to a target **nucleic acid** strand. The A-form geometry imparts properties to the **oligonucleotide** that modulate binding affinity and **nuclease resistance**. By utilizing C2' endo sugars or O4' endo sugars, the B-form characteristics are imparted to a portion of the **oligonucleotide**. The A-form characteristics are imparted via use of either **2'-O-modified** nucleotides that have 3' endo geometries or use of end caps having particular nuclease stability or by use of both of these in conjunction with each other.

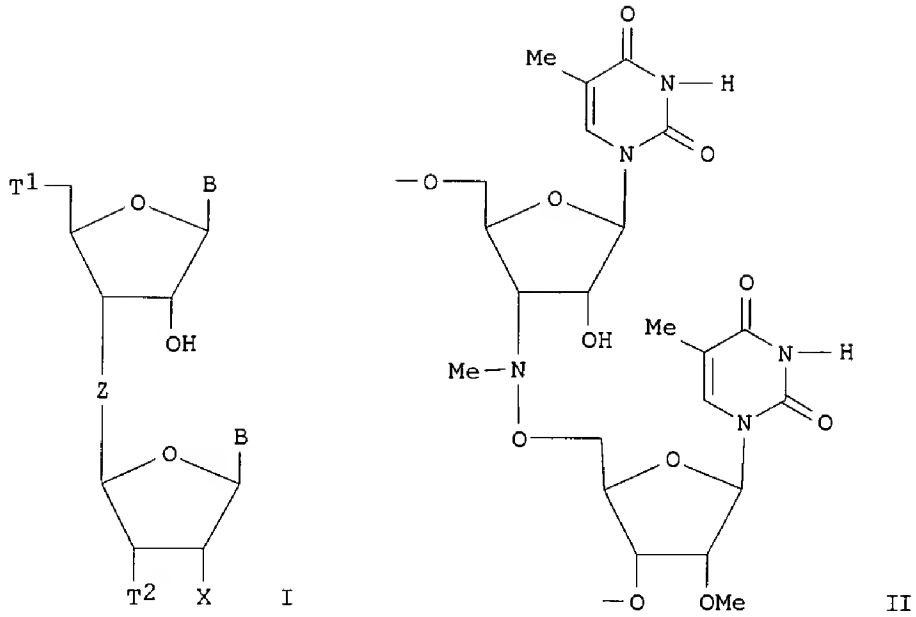
L14 ANSWER 2 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 137:63428 CA
TITLE: Preparation, **nuclease resistance**, and protein binding of **oligonucleotide** analogs having **modified** dimers
INVENTOR(S): Cook, Phillip Dan; Manoharan, Muthiah; Bhat, Balkrishen
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: U.S., 33 pp., Cont.-in-part of U. S. Ser. No. 248,386.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 100
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6420549	B1	20020716	US 1998-131102	19980807
US 5859221	A	19990112	US 1995-468037	19950606
US 5965722	A	19991012	US 1997-848840	19970430
AU 713740	B2	19991209	AU 1997-26244	19970624
AU 9726244	A1	19971106		
US 6232463	B1	20010515	US 1998-128508	19980804
US 6359124	B1	20020319	US 1999-248386	19990212

WO 2000008214 A1 20000217 WO 1999-US18023 19990806
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 9953448 A1 20000228 AU 1999-53448 19990806
PRIORITY APPLN. INFO.:

US 1995-468037	A2	19950606
US 1997-848840	A3	19970430
US 1999-248386	A2	19990212
US 1990-463358	B2	19900111
US 1990-566977	B2	19900813
US 1991-801168	B1	19911120
US 1991-814961	B2	19911224
US 1992-835932	A2	19920305
US 1992-854634	B2	19920701
US 1992-958134	B2	19921005
WO 1992-US11339	B1	19921223
US 1993-7996	B2	19930121
AU 1993-38025	A3	19930225
US 1993-39979	B1	19930330
US 1993-40526	A2	19930331
US 1993-40903	A3	19930331
US 1993-40933	B1	19930331
WO 1993-US9346	B1	19931001
US 1994-227180	A2	19940413
US 1994-244993	A2	19940621
US 1994-300072	A3	19940902
US 1994-317289	A2	19941003
US 1994-335046	A2	19941107
US 1995-411734	A2	19950403
US 1995-465866	A2	19950606
US 1995-488256	A2	19950607
US 1997-794493	A2	19970204
US 1997-948151	A1	19971009
US 1998-131102	A	19980807
WO 1999-US18023	W	19990806

OTHER SOURCE(S): MARPAT 137:63428
GI



AB Modified dimers having a ribose sugar moiety in the 5'-nucleoside and a **2'-modified** sugar in the 3'-nucleoside I wherein Z is a covalent inter-sugar linkage; each T1 and T2 are independently, OH, OR, CH2R, NHR, SH, SR, or a blocked hydroxyl; B is a heterocyclic base; X is F, OR, SR or -NRR2; R is **alkyl**, or a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur and wherein said ring system is aliph., unsatd. aliph., arom. or heterocyclic; and wherein any available hydrogen atom of said ring system is each replaceable with an **alkoxy**, **alkylamino**, urea or **alkylurea** group; are provided. The modified dimers are useful in the prepn. of oligonucleotide analogs having enhanced properties compared to native oligonucleotides, including increased **nuclease resistance**, enhanced binding affinity and improved protein binding. Thus, GTCGTACC-II-TCCGGTCC was prepd. and tested for its serum and cytoplasmic **nuclease resistance** (no data).

REFERENCE COUNT: 161 THERE ARE 161 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 137:33492 CA
TITLE: Synthesis of **2'-O-modified** nucleosides via regioselective **alkylation** and their incorporation into oligodeoxyribonucleotides having improved hybridization affinity and **nuclease resistance**
INVENTOR(S): Kawasaki, Andrew M.; Fraser, Allister S.; Manoharan, Muthiah; Cook, P. Dan; Prakash, Thazha P.
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: U.S., 24 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6403779	B1	20020611	US 1999-227782	19990108

PRIORITY APPLN. INFO.: US 1999-227782 19990108
OTHER SOURCE(S): CASREACT 137:33492; MARPAT 137:33492
AB Methods for the regioselective **alkylation** at the 2'-hydroxy position over the 3'-hydroxy position of nucleosides and nucleoside analogs, forming **2'-O-ester modified** compds., are disclosed. Redn. and derivatization of the **2'-O-ester** provides **2'-O-modified** nucleosides and nucleoside analogs useful for the synthesis of oligomeric compds. having improved hybridization affinity and **nuclease resistance**. Thus, 5'-O-t-butyldiphenylsilyl-2'-O-(piperidinyl-N-oxyethyl)-5-methyluridine was prepd. and incorporated into oligodeoxyribonucleotides.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 67 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002484118 MEDLINE
DOCUMENT NUMBER: 22231016 PubMed ID: 12269806
TITLE: **2'-O-[2-(methylthio)ethyl]-modified oligonucleotide**: an analogue of **2'-O-[2-(methoxy)-ethyl]-modified oligonucleotide** with improved protein binding properties and high binding affinity to target RNA.
AUTHOR: Prakash Thazha P; Manoharan Muthiah; Kawasaki Andrew M; Fraser Allister S; Lesnik Elena A; Sioufi Namir; Leeds Janet M; Teplova Marianna; Egli Martin
CORPORATE SOURCE: Department of Medicinal Chemistry, Isis Pharmaceuticals, 2292 Faraday Ave, Carlsbad, CA 92008, USA.
CONTRACT NUMBER: GM 55237 (NIGMS)
SOURCE: BIOCHEMISTRY, (2002 Oct 1) 41 (39) 11642-8. Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1MLX
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20020925
Last Updated on STN: 20021213
Entered Medline: 20021119

AB A novel **2'-modification, 2'-O-[2-(methylthio)ethyl]** or 2'-O-MTE, has been incorporated into **oligonucleotides** and evaluated for properties relevant to **antisense** activity. The results were compared with the previously characterized 2'-O-[2-(methoxy)ethyl] **2'-O-MOE modification**. As expected, the **2'-O-MTE modified oligonucleotides** exhibited improved binding to human serum albumin compared to the **2'-O-MOE modified oligonucleotides**. The **2'-O-MTE oligonucleotides** maintained high binding affinity to target RNA. Nuclease digestion of 2'-O-MTE **oligonucleotides** showed that they have limited **resistance** to exonuclease **degradation**. We analyzed the crystal structure of a decamer DNA duplex containing the **2'-O-MTE modifcation**. Analysis of the crystal structure provides insight into the improved RNA binding affinity, protein binding affinity and limited resistance of **2'-O-MTE modified oligonucleotides** to exonuclease degradation.

L14 ANSWER 5 OF 67 SCISEARCH COPYRIGHT 2003 ISI (R)

ACCESSION NUMBER: 2002:703411 SCISEARCH
THE GENUINE ARTICLE: 584TL
TITLE: Nucleosides and nucleotides. Part 214: Thermal stability of triplexes containing 4 'alpha-C-**aminoalkyl**-2 '-deoxynucleosides
AUTHOR: Atsumi N; Ueno Y; Kanazaki M; Shuto S; Matsuda A (Reprint)
CORPORATE SOURCE: Hokkaido Univ, Grad Sch Pharmaceut Sci, Kita Ku, Kita 12, Nishi 6, Sapporo, Hokkaido 0600812, Japan (Reprint); Hokkaido Univ, Grad Sch Pharmaceut Sci, Kita Ku, Sapporo, Hokkaido 0600812, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: BIOORGANIC & MEDICINAL CHEMISTRY, (SEP 2002) Vol. 10, No. 9, pp. 2933-2939.
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND.
ISSN: 0968-0896.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 36

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In order to develop novel antigene molecules forming thermally stable triplexes with target DNAs and having **nuclease resistance** properties, e synthesized oligodeoxynucleotides (ODNs) with various lengths of **aminoalkyl**-linkers at the 4'alpha position of thymidine and the **aminoethyl**-linker at the 4'alpha position of 2'-deoxy-5-methylcytidine. Thermal stability of triplexes between these ODNs and a DNA duplex was studied by thermal denaturation. The ODNs containing the nucleoside 2 with the **aminoethyl**-tinker or the nucleoside 3 with the **aminopropyl**-linker thermally stabilized the triplexes. whereas the ODNs containing the nucleoside I with the **aminomethyl**-linker or the nucleoside 4 with the 2-[N-(2-**aminoethyl**)carbamoyl]oxy]ethyl-linker thermally destabilized the triplexes. The ODNs containing 2 were tile most efficient at stabilizing the triplexes with the target DNA. The ODNs containing 4'alpha-C-(2-**aminoethyl**)-2'-deoxy-5-methylcytidine (5) also efficiently stabilized the triplexes with the target DNA. Stability of the ODN containing 5 to nucleolytic hydrolysis by snake venom phosphodiesterase (a 3'-exonuclease) was Studied. It was found that the ODN containing 5 was more **resistant** to **nucleolytic** digestion by the enzyme than all unmodified ODN. In a previous paper, we reported that the ODNs containing 2 were more **resistant** to **nucleolytic** digestion by DNase I (an endonuclease) than the Unmodified ODNs. Thus, it was found that the ODNs containing 4'alpha-C-(2-**aminoethyl**)-2'-deoxynucleosides were good candidates for antigene molecules.

L14 ANSWER 6 OF 67 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2002072653 MEDLINE
DOCUMENT NUMBER: 21657369 PubMed ID: 11798305
TITLE: Synthesis of 2'-O-[2-[(N,N-dimethylamino)oxy]ethyl] **modified** nucleosides and **oligonucleotides**.
AUTHOR: Prakash Thazha P; Kawasaki Andrew M; Fraser Allister S; Vasquez Guillermo; Manoharan Muthiah
CORPORATE SOURCE: Department of Medicinal Chemistry, Isis Pharmaceuticals Inc., 2292 Faraday Avenue, Carlsbad, California 92008, USA.
SOURCE: JOURNAL OF ORGANIC CHEMISTRY, (2002 Jan 25) 67 (2) 357-69. Journal code: 2985193R. ISSN: 0022-3263.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020404
Entered Medline: 20020402

AB A versatile synthetic route has been developed for the synthesis of 2'-O-[2-[(N,N-dimethylamino)oxy]ethyl] (abbreviated as **2'-O-DMAOE**) **modified** purine and pyrimidine nucleosides and their corresponding nucleoside phosphoramidites and solid supports. To synthesize 2'-O-DMAOE purine nucleosides, the key intermediate B (Scheme 1) was obtained from the 2'-O-allyl purine nucleosides (13a and 15) via oxidative cleavage of the carbon-carbon bond to the corresponding aldehydes followed by reduction. To synthesize pyrimidine nucleosides, opening the 2,2'-anhydro-5-methyluridine 5 with the borate ester of ethylene glycol gave the key intermediate B. The 2'-O-(2-hydroxyethyl) nucleosides were converted, in excellent yield, by a regioselective Mitsunobu reaction, to the corresponding 2'-O-[2-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)oxy]ethyl] nucleosides (18, 19, and 20). These compounds were subsequently deprotected and converted into the 2'-O-[2-[(methyleneamino)oxy]ethyl] derivatives (22, 23, and 24). Reduction and a second reductive amination with formaldehyde yielded the corresponding 2'-O-[2-[(N,N-dimethylamino)oxy]ethyl] nucleosides (25, 26, and 27). These nucleosides were converted to their 3'-O-phosphoramidites and controlled-pore glass solid supports in excellent overall yield. Using these monomers, **modified oligonucleotides** containing pyrimidine and purine bases were synthesized with phosphodiester, phosphorothioate, and both linkages (phosphorothioate and phosphodiester) present in the same **oligonucleotide** as a chimera in high yields. The **oligonucleotides** were characterized by HPLC, capillary gel electrophoresis, and ESMS. The effect of this **modification** on the affinity of the **oligonucleotides** for **complementary** RNA and on nuclease stability was evaluated. The **2'-O-DMAOE modification** enhanced the binding affinity of the **oligonucleotides** for the **complementary** RNA (and not for DNA). The **modified oligonucleotides** that possessed the phosphodiester backbone demonstrated excellent **resistance** to **nuclease** with t(1/2) > 24 h.

L14 ANSWER 7 OF 67 MEDLINE
ACCESSION NUMBER: 2001691008 MEDLINE
DOCUMENT NUMBER: 21599647 PubMed ID: 11738576
TITLE: 2'-O,4'-C-ethylene-bridged **nucleic acids** (ENA): highly **nuclease-resistant** and thermodynamically stable **oligonucleotides** for **antisense** drug.
AUTHOR: Morita Koji; Hasegawa Chikako; Kaneko Masakatsu; Tsutsumi Shinya; Sone Junko; Ishikawa Tomio; Imanishi Takeshi; Koizumi Makoto
CORPORATE SOURCE: Exploratory Chemistry Research Laboratories, Sankyo Co., Ltd., 140-8710, Tokyo, Japan.
SOURCE: BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, (2002 Jan 7) 12 (1) 73-6.
Journal code: 9107377. ISSN: 0960-894X.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20011213
Last Updated on STN: 20021008
Entered Medline: 20021004

AB To develop **antisense oligonucleotides**, novel nucleosides, 2'-O,4'-C-ethylene nucleosides and their corresponding

phosphoramidites, were synthesized as building blocks. The 1H NMR analysis showed that the 2'-O,4'-C-ethylene linkage of these nucleosides restricts the sugar puckering to the N-conformation as well as the linkage of 2'-O,4'-C-methylene nucleosides which are known as bridged **nucleic acids** (BNA) or locked **nucleic acids** (LNA). The ethylene-bridged **nucleic acids** (ENA) showed a high binding affinity for the complementary RNA strand (DeltaT(m)=+5.2 degrees C/**modification**) and were more **nuclease-resistant** than natural DNA and BNA/LNA. These results indicate that ENA have better properties as **antisense oligonucleotides** than BNA/LNA.

L14 ANSWER 8 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 137:305342 CA
TITLE: Real-time monitoring of rolling-circle amplification using a **modified** molecular beacon design
AUTHOR(S): Nilsson, Mats; Gullberg, Mats; Dahl, Fredrik; Szuhai, Karoly; Raap, Anton K.
CORPORATE SOURCE: Department of Molecular Cell Biology, Leiden University Medical Center, Leiden, 2333 AL, Neth.
SOURCE: Nucleic Acids Research (2002), 30(14), e66/1-e66/7
CODEN: NARHAD; ISSN: 0305-1048
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We describe a method to monitor rolling-circle replication of circular **oligonucleotides** in dual-color and in real-time using mol. beacons. The method can be used to study the kinetics of the polymn. reaction and to amplify and quantify circularized **oligonucleotide** probes in a rolling-circle amplification (RCA) reaction. **Modified** mol. beacons were made of **2'**-O-Me-RNA to prevent 3' exonucleolytic degrdn. by the polymerase used. Moreover, the complement of one of the stem sequences of the mol. beacon was included in the RCA products to avoid fluorescence quenching due to inter-mol. hybridization of neighboring mol. beacons hybridizing to the concatemeric polymn. product. The method allows highly accurate quantification of circularized DNA over a broad concn. range by relating the signal from the test DNA circle to an internal ref. DNA circle reporting in a distinct fluorescence color.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 9 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 134:276474 CA
TITLE: **Nucleic acid** arrays using **modified oligonucleotides** with improved binding affinity and acid stability and **nuclease resistance**
INVENTOR(S): Dale, Roderic M. K.
PATENT ASSIGNEE(S): Oligos Etc. Inc., USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001023620	A2	20010405	WO 2000-US26989	20000928
WO 2001023620	A3	20011018		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6440723 B1 20020827 US 2000-528404 20000317

PRIORITY APPLN. INFO.: US 1999-408761 A 19990929
US 2000-524092 A 20000313
US 2000-528404 A 20000317
US 1998-223498 A2 19981230
US 1999-408088 A2 19990929

AB The present invention provides arrays having assocd. **modified oligonucleotides** which are acid-stable, backbone-**modified**, and end-blocked, methods of making such arrays, assays for using such arrays, and kits contg. such arrays. The **modified** structures comprise 1', **2'**, 3', or 5' position **modifying**-groups and/or **modifying** the ribose oxygen; specific examples are provided comparing the stability of **oligonucleotides** contg. 2'-O-Me, 2'-O-Et, or 2'-ethoxymethoxy groups, as well as 5'-end butanol and 3'-end Bu blocking groups, with unmodified DNA and/or RNA. In one embodiment, the assocd. **nucleic acids** of the array of the invention exhibit substantial acid resistance, allowing the arrays to be treated with low pH solns. In another embodiment, the **modified** assocd. **nucleic acids** of the array of the invention exhibit substantial **resistance** to **nuclease degrdn.**

L14 ANSWER 10 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 135:117895 CA
TITLE: A **modified** SELEX method that minimizes the contribution of fixed end sequences to target binding
INVENTOR(S): Pagratis, Nikos; Gold, Larry; Shtatland, Timur; Javornik, Brenda
PATENT ASSIGNEE(S): Gilead Sciences, Inc., USA
SOURCE: U.S., 160 pp., Cont.-in-part of U.S. 5,475,096. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 119
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6261774	B1	20010717	US 1999-275850	19990324
US 5475096	A	19951212	US 1991-714131	19910610
EP 786469	A2	19970730	EP 1997-200035	19910610
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
IL 112141	A1	19980405	IL 1991-112141	19910611
WO 2000056930	A1	20000928	WO 2000-US7486	20000320
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2003003461	A1	20030102	US 2001-907111	20010717

PRIORITY APPLN. INFO.: US 1990-536428 B2 19900611
US 1991-714131 A2 19910610
EP 1991-912753 A3 19910610
IL 1991-98456 A3 19910611
US 1999-275850 A 19990324

AB This invention is directed to a method for identifying **nucleic acid** ligands by the SELEX method wherein the participation of fixed sequences in target binding is eliminated or minimized. The method involves changing the fixed sequences within the **oligonucleotides** during the amplification step of a round of selection and amplification. Methods of exchanging the const. regions are described. Typically, a restriction site at the junction of the fixed and variable sequences is introduced during the amplification stage and is used to remove the fixed regions. After cleavage the variable regions are purified electrophoretically, overhanging ends are filled in and new fixed sequences attached by blunt end ligation. Only one of the strands will be phosphorylated to allow ligation of the fixed sequence. The use of the method is demonstrated by selection of ligands for vascular endothelial growth factor. The recovered sequences were largely similar to those found by prior art methods but appear to lack artifactual sequences resulting from fixed sequence contribution.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 11 OF 67 MEDLINE
ACCESSION NUMBER: 2001151489 MEDLINE
DOCUMENT NUMBER: 21104616 PubMed ID: 11181921
TITLE: Pharmacokinetic properties of **2'-O-(2-methoxyethyl)-modified oligonucleotide** analogs in rats.
AUTHOR: Geary R S; Watanabe T A; Truong L; Freier S; Lesnik E A; Sioufi N B; Sasmor H; Manoharan M; Levin A A
CORPORATE SOURCE: Isis Pharmaceuticals, Inc., Carlsbad, California 92008, USA.. rgeary@isisph.com
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (2001 Mar) 296 (3) 890-7.
Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010315

AB Plasma pharmacokinetics, biodistribution, excretion, and metabolism of four **modified** 20-mer **antisense oligonucleotides** targeted to human intercellular adhesion molecule-1 mRNA have been characterized in rats and compared with a first-generation phosphorothioate oligodeoxynucleotide (PS ODN), ISIS 2302. The **modified oligonucleotides** contained **2'-O-(2-methoxyethyl)** (**2'-O-MOE**) ribose sugar **modifications** on all or a portion of the nucleotides in the antisense sequence. The **2'-O-MOE-modified oligonucleotides** were **resistant** to **nuclease** metabolism in both plasma and tissue. In general, plasma pharmacokinetics was not substantially altered by addition of the **2'-O-MOE modification** to PS ODN. Thus, plasma clearance was dominated by distribution to tissues, broadly, with less than 10% of the administered dose excreted in urine or feces over 24 h. However, the **2'-O-MOE modification** combined with the phosphodiester (PO) backbone exhibited 10-fold more rapid plasma clearance, with approximately 50% of

the dose excreted in urine as intact oligonucleotide. Consistent with its rapid and extensive excretion, the PO **2'-O-MOE modification** distributed to very few organs in any substantial amount with the exception of the kidney. Oligonucleotides that contained phosphorothioate backbones were highly bound to plasma proteins. Indeed, the primary characteristic that resulted in the most marked alterations in pharmacokinetics appeared to be the affinity and capacity of these compounds to bind plasma proteins. A balance of greater stability supplied by the **2'-O-MOE modification** together with maintenance of plasma protein binding appears to be necessary to ensure favorable pharmacokinetics of this new generation of antisense oligonucleotides.

L14 ANSWER 12 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 136:263373 CA
TITLE: 2'-O,4'-C-ethylene-bridged **nucleic acids** (ENA): highly **nuclease-resistant** and thermodynamically stable **oligonucleotides** for **antisense** drug
AUTHOR(S): Morita, Koji; Hasegawa, Chikako; Kaneko, Masakatsu; Tsutsumi, Shinya; Sone, Junko; Ishikawa, Tomio; Imanishi, Takeshi; Koizumi, Makoto
CORPORATE SOURCE: Sankyo Co., Ltd., Exploratory Chemistry Research Laboratories, Tokyo, 140-8710, Japan
SOURCE: Bioorganic & Medicinal Chemistry Letters (2001), Volume Date 2002, 12(1), 73-76
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To develop **antisense oligonucleotides**, novel nucleosides, 2'-O,4'-C-ethylene nucleosides and their corresponding phosphoramidites, were synthesized as building blocks. The 1H NMR anal. showed that the 2'-O,4'-C-ethylene linkage of these nucleosides restricts the sugar puckering to the N-conformation as well as the linkage of 2'-O,4'-C-methylene nucleosides which are known as bridged **nucleic acids** (BNA) or locked **nucleic acids** (LNA). The ethylene-bridged **nucleic acids** (ENA) showed a high binding affinity for the complementary RNA strand (.DELTA.Tm=+5.**2** .degree.C/**modification**) and were more **nuclease-resistant** than natural DNA and BNA/LNA. These results indicate that ENA have better properties as **antisense oligonucleotides** than BNA/LNA.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 13 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
ACCESSION NUMBER: 2001:162469 BIOSIS
DOCUMENT NUMBER: PREV200100162469
TITLE: Arrays with **modified oligonucleotide** and polynucleotide compositions.
AUTHOR(S): Dale, Roderic M. K.
ASSIGNEE: Oligos Etc. Inc., Wilsonville, OR, USA
PATENT INFORMATION: US 6087112 July 11, 2000
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (July 11, 2000) Vol. 1236, No. 2, pp. No Pagination. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
AB The present invention provides arrays having associated **modified oligonucleotides**, e.g., **2'-O-R oligonucleotides**

, methods of making such arrays, assays for using such arrays, and kits containing such arrays. In one embodiment, the arrays of the invention exhibit an increased binding affinity with **complementary nucleic acids**, and in particular with complementary RNA. In another embodiment, the associated **nucleic acids** of the array of the invention exhibit substantial acid resistance, allowing the arrays to be treated with low pH solutions. In another embodiment, the **modified** associated **nucleic acids** of the array of the invention exhibit substantial **resistance** to **nuclease degradation**.

L14 ANSWER 14 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 133:359771 CA
TITLE: **Oligonucleotide** and polynucleotide arrays **modified** for improved stability
INVENTOR(S): Dale, Roderic M. K.
PATENT ASSIGNEE(S): Oligos Etc. Inc., USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000070093	A1	20001123	WO 2000-US13185	20000511

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-311113 A 19990513

AB The present invention provides arrays having assocd. **modified oligonucleotides**, methods of making such arrays, assays for using such arrays, and kits contg. such arrays. The **modified** structures comprise 1', **2'**, 3', or 5' position **modifying** -groups and/or **modifying** the ribose oxygen; specific examples are provided comparing the stability of **oligonucleotides** contg. 2'-O-Me, 2'-O-Et, or 2'-ethoxymethoxy groups, as well as 5'-end butanol and 3'-end Bu blocking groups, with unmodified DNA and/or RNA. In one embodiment, the arrays of the invention exhibit an increased binding affinity with **complementary nucleic acids**, and in particular with complementary RNA. In another embodiment, the assocd. **nucleic acids** of the array of the invention exhibit substantial acid resistance, allowing the arrays to be treated with low pH solns. In another embodiment, the **modified** assocd. **nucleic acids** of the array of the invention exhibit substantial **resistance** to **nuclease degrdn**.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 15 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 133:350465 CA
TITLE: Preparation of **oligonucleotides** having A-DNA form and B-DNA form conformational geometry as substrates for RNase H and **nuclease resistance**

INVENTOR(S): Manoharan, Muthiah; Mohan, Venkatraman
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 132 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000066609	A1	20001109	WO 2000-US11913	20000503
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6369209	B1	20020409	US 1999-303586	19990503
EP 1180113	A1	20020220	EP 2000-928716	20000503
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002543215	T2	20021217	JP 2000-615638	20000503

PRIORITY APPLN. INFO.: US 1999-303586 A 19990503
WO 2000-US11913 W 20000503

AB **Modified oligonucleotides** contg. both A-form conformation geometry and B-form conformation geometry nucleotides are disclosed. The B-form geometry allows the **oligonucleotide** to serve as substrates for RNase H when bound to a target **nucleic acid** strand. The A-form geometry imparts properties to the **oligonucleotide** that modulate binding affinity and **nuclease resistance**. By utilizing C2' endo sugars or O4' endo sugars, the B-form characteristics are imparted to a portion of the **oligonucleotide**. The A-form characteristics are imparted via use of either 2'-O-**modified** nucleotides that have 3' endo geometries or use of end caps having particular nuclease stability or by use of both of these in conjunction with each other.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 16 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 133:346230 CA
TITLE: Covalent **modification** of **2** '-hydroxyl groups of RNA
INVENTOR(S): Goldsborough, Andrew Simon
PATENT ASSIGNEE(S): Cyclops Genome Sciences Limited, UK
SOURCE: PCT Int. Appl., 184 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000066605	A2	20001109	WO 2000-GB1687	20000502
WO 2000066605	A3	20010426		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,				

ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,
ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

WO 2001094626 A1 20011213 WO 2000-GB1683 20000502
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR,
CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,
ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1196631 A1 20020417 EP 2000-929665 20000502
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO

US 2003039985 A1 20030227 US 2001-11495 20011026

PRIORITY APPLN. INFO.: GB 1999-10154 A 19990430
GB 1999-10156 A 19990430
GB 1999-10157 A 19990430
GB 1999-10158 A 19990430
WO 2000-GB1683 W 20000502

AB Provided is a polynucleotide comprising mRNA, rRNA or viral RNA, greater than 25 % of the ribose rings of which are covalently **modified** at the **2'** - OH position. Further provided is a method for producing a double-stranded **oligo-** or polynucleotide from a template, which comprises contacting the template with a plurality of mononucleotides comprising UTP, dTTP and/or dUTP, ATP and/or dATP, GTP and/or dGTP, and CTP and/or dCTP, in the presence of a **nucleic acid** polymerase and optionally a template primer under conditions to polymerize the mononucleotides to form a **nucleic acid** strand **complementary** to the template, wherein the template comprises an **oligo-** or polyribonucleotide, a proportion of the ribose rings of which are covalently **modified** at the **2** ' - OH position to bear a substituent which enables replication of the template by the **nucleic acid** polymerase. Also provided is use of a polynucleotide comprising mRNA, rRNA or viral RNA, a proportion of the ribose rings of which are covalently **modified** at the **2'** - OH position, in a hybridization reaction. Thus, numerous methods for chem. **modifying** RNA (e.g., acylation, **halogenation**) are provided. The effect of **modifications** on **resistance** to **nuclease** digestion and on hybridization and replication are detd.

L14 ANSWER 17 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 133:99558 CA
TITLE: **Modified antisense oligonucleotides** for inhibiting phosphodiesterase 4 gene expression and the therapeutic uses thereof
INVENTOR(S): Dale, Roderic M. K.; Arrow, Amy; Thompson, Terry
PATENT ASSIGNEE(S): Oligos Etc. Inc., USA
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000040714	A2	20000713	WO 1999-US29976	19991215
WO 2000040714	A3	20001102		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2357950	AA	20000713	CA 1999-2357950	19991215
EP 1141278	A2	20011010	EP 1999-968130	19991215

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

JP 2002534086	T2	20021015	JP 2000-592411	19991215
US 2003045490	A1	20030306	US 2002-76597	20020219

PRIORITY APPLN. INFO.:	US 1998-223586	A	19981230
	US 1999-364626	A	19990729
	WO 1999-US29976	W	19991215

AB The invention provides end-blocked acid resistant antisense oligonucleotides targeted at inhibiting expression of genes coding for Phosphodiesterase 4 (PDE4). The oligonucleotides of this invention exhibit substantial stability at low pH, substantial **resistance** to **nuclease degrdn.**, low toxicity and binding specificity both in vivo and in vitro. The invention further relates to the therapeutic uses of oligonucleotides of this invention in treatment of PDE4-mediated diseases.

L14 ANSWER 18 OF 67 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER:	132:152089 CA
TITLE:	Preparation, **nuclease resistance**, and protein binding of **oligonucleotide** analogs having **modified** dimers
INVENTOR(S):	Cook, Phillip Dan; Manoharan, Muthiah; Bhat, Balkrishen
PATENT ASSIGNEE(S):	Isis Pharmaceuticals, Inc., USA
SOURCE:	PCT Int. Appl., 105 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	100

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000008214	A1	20000217	WO 1999-US18023	19990806

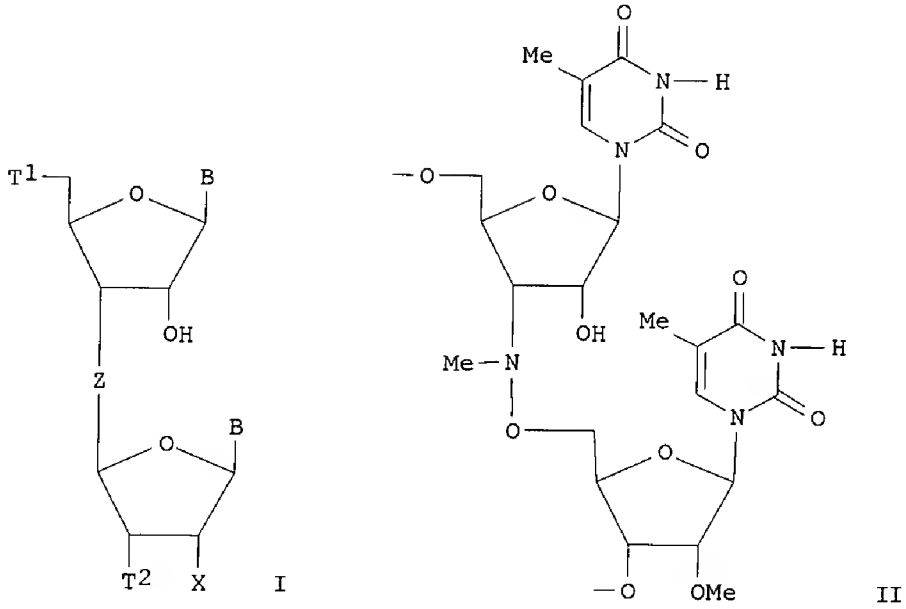
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 713740	B2	19991209	AU 1997-26244	19970624
AU 9726244	A1	19971106		
US 6232463	B1	20010515	US 1998-128508	19980804

US 6420549	B1	20020716	US 1998-131102		19980807
AU 9953448	A1	20000228	AU 1999-53448		19990806
PRIORITY APPLN. INFO.:			US 1998-131102	A	19980807
			AU 1993-38025	A3	19930225
			US 1995-468037	A2	19950606
			US 1997-848840	A3	19970430
			US 1997-948151	A1	19971009
			US 1999-248386	A2	19990212
			WO 1999-US18023	W	19990806

OTHER SOURCE(S): MARPAT 132:152089
GI



I II

AB Modified dimers having a ribose sugar moiety in the 5'-nucleoside and a **2'-modified** sugar in the 3'-nucleoside I wherein Z is a covalent inter-sugar linkage; each T1 and T2 is, independently, OH, OR1, CH2R1, NHR1, SH, SR1, or a blocked hydroxyl; R1 is **alkyl**; Bx is a heterocyclic base; X is F, OR, SR or -NRR2; R is **alkyl**, or a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur and wherein said ring system is aliph., unsatd. aliph., arom. or heterocyclic; and wherein any available hydrogen atom of said ring system is each replaceable with an **alkoxy**, **alkylamino**, urea or **alkylurea** group; are provided. The modified dimers are useful in the prepn. of oligonucleotide analogs having enhanced properties compared to native oligonucleotides, including increased **nuclease resistance**, enhanced binding affinity and improved protein binding. Thus, GTCGTACC-II-TCCGGTCC was prepd. and tested for its serum and cytoplasmic **nuclease resistance** (no data).

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 19 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 132:133889 CA

TITLE: **Oligonucleotides** containing 2',5'-linkages with improved **nuclease resistance** and **nucleic acid** binding
INVENTOR(S): Manoharan, Muthiah; Cook, Phillip Dan
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000004189	A1	20000127	WO 1999-US15886	19990713
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9953149	A1	20000207	AU 1999-53149	19990713

PRIORITY APPLN. INFO.: US 1998-115043 A 19980714
WO 1999-US15886 W 19990713

AB **Modified oligonucleotides** contg. at least one **2'**,5'-internucleotide linkage are provided. The **oligonucleotides** of the invention may also bear addnl. substituents at the 3'-position. Thus, the 20-nucleotide phosphorothioate-linked **oligodeoxyribonucleotide** ATGCATTCTGCCCCCAAGGA inhibited c-raf expression in bEND cells. **Modification** of this 20-mer to contain 3'-terminal 2'-5' linked 3'-O-(2-methoxyethyl)deoxyribonucleosides resulted in an **oligonucleotide** with comparable biol. activity by increased **resistance** to **nuclease degrdn.** in vivo (in mice).

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 20 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 133:350466 CA
TITLE: Preparation of **2'**-O-acetamido **modified** nucleosides and **oligodeoxyribonucleotide** duplexes
INVENTOR(S): Manoharan, Muthiah; Kawasaki, Andrew M.; Cook, Phillip Dan; Fraser, Allister S.; Prakash, Thazha P.
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: U.S., 29 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6147200	A	20001114	US 1999-378568	19990819
WO 2001014400	A1	20010301	WO 2000-US22443	20000816
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,				

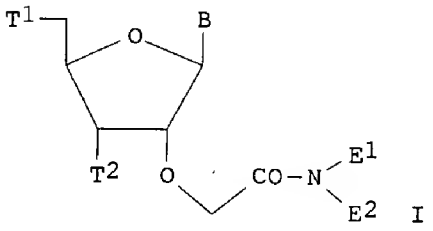
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1212339 A1 20020612 EP 2000-955583 20000816
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL

PRIORITY APPLN. INFO.: US 1999-378568 A2 19990819
WO 2000-US22443 W 20000816

OTHER SOURCE(S): MARPAT 133:350466

GI



I

AB Nucleosidic monomers and **oligomeric** compds. prepd. therefrom are provided. Also provided is a novel method of deprotection of **oligomeric** compds. **Oligomeric** compds. having at least one **2'-O-acetamido modified** nucleosidic monomer I wherein B is an optionally protected heterocyclic base moiety; each T1 and T2 is, independently, OH, a protected hydroxyl; or one of T1 and T2 is OH or a protected hydroxyl and the other of T1 and T2 is a solid support or an activated phosphorus-contg. substituent group; each E1 and E2 is, independently, **alkyl**, or one of E1 and E2 is H and the other of E1 and E2 is CH3 ; or each E1 and E2 is, independently, H, **alkylidene, thioalkyl**, a polypeptide having from 2 to 10 peptide linked **amino** acids, a folic acid moiety optionally bearing a linking group attaching said folic acid moiety from the .alpha. or .gamma. carboxyl group to the 2'-substituent wherein said linking group is -NH-(CH2)6-, or a cholesterol moiety optionally bearing a linking group attaching said cholesterol moiety from the hydroxyl group to the 2'-substituent, wherein said linking group is -C(O)NH(CH2)6-, provided that only one of E1 and E2 is H, are expected to have increased **nuclease resistance** and binding affinity to a **complementary** strand of **nucleic acid**. Such **oligomeric** compds. are useful for diagnostics and other research purposes, for modulating the expression of a protein in organisms, and for the diagnosis, detection and treatment of other conditions responsive to **oligonucleotide** therapeutics. Thus, 5'-O-(4,4'-dimethoxytrityl)-2'-O-(2-N-methylacetamido)-5-methyluridine was prepd. and incorporated into **oligodeoxyribonucleotide** duplexes. The **oligomeric** compds. of the present invention are expected to have enhanced **nuclease resistance** and superior hybridization properties.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 21 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 133:173003 CA

TITLE: **Modified oligoribonucleotides** which stimulate double-stranded RNase activity and their use for targeted in vivo RNA cleavage
INVENTOR(S): Crooke, Stanley T.
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: U.S., 44 pp., Cont.-in-part of U. S. 5,898,031.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6107094	A	20000822	US 1997-870608	19970606
US 5898031	A	19990427	US 1996-659440	19960606
US 2002164601	A1	20021107	US 2001-900425	20010706
US 2003044941	A1	20030306	US 2002-79185	20020220

PRIORITY APPLN. INFO.: US 1996-659440 A2 19960606
US 1997-870608 A3 19970606
US 2000-479783 A2 20000107
US 2001-900425 A2 20010706

AB **Oligomeric** compds. including **oligoribonucleotides** and **oligoribonucleosides** are provided that have subsequences of 2'-pentoribofuranosyl nucleosides that activate dsRNase. The **oligoribonucleotides** and **oligoribonucleosides** can include substituent groups for increasing binding affinity to **complementary nucleic acid** strand as well as substituent groups for increasing **nuclease resistance**. The **oligomeric** compds. are useful for diagnostics and other research purposes, for modulating the expression of a protein in organisms, and for the diagnosis, detection and treatment of other conditions susceptible to **oligonucleotide** therapeutics. Also included in the invention are mammalian RNases, i.e., enzymes that degrade RNA, and substrates for such RNases. Such a RNase is referred to herein as a dsRNase, wherein "ds" indicates the RNase's specificity for certain double-stranded RNA substrates. The artificial substrates for the dsRNases described herein are useful in prepg. affinity matrixes for purifying mammalian RNase as well as non-degradative RNA-binding proteins.
REFERENCE COUNT: 165 THERE ARE 165 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 22 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4
ACCESSION NUMBER: 2000:324544 BIOSIS
DOCUMENT NUMBER: PREV200000324544
TITLE: Zwitterionic oligonucleotides with 2'-O-(3-(N,N-dimethylamino)propyl)-RNA modification: Synthesis and properties.
AUTHOR(S): Prakash, Thazha P.; Manoharan, Muthiah (1); Fraser, Allister S.; Kawasaki, Andrew M.; Lesnik, Elena A.; Owens, Stephen R.
CORPORATE SOURCE: (1) Department of Medicinal Chemistry, Isis Pharmaceuticals, 2292 Faraday Ave, Carlsbad, CA, 92008 USA
SOURCE: Tetrahedron Letters, (19 June, 2000) Vol. 41, No. 25, pp. 4855-4859. print.
ISSN: 0040-4039.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A novel **2'-modification, 2**

'-O-(3-(N,N-dimethylamino)propyl) or 2'-O-DMAP, has been incorporated into oligonucleotides and compared to the known 2'-O-(3-**aminopropyl**) or **2**'-O-AP **modification** for **antisense** properties. The **2**'-O-DMAP **modified oligonucleotides** exhibit very high **nuclease resistance** like the **2**'-O-AP **modification** due to the 'charge effect' and maintain high binding affinity to target RNA relative to known **modifications** when a few **2**'-O-DMAP residues are dispersed throughout the oligonucleotide.

L14 ANSWER 23 OF 67 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 2000:245312 SCISEARCH
THE GENUINE ARTICLE: 296ZT
TITLE: Highly **nuclease-resistant** phosphodiester-type oligodeoxynucleotides containing 4'alpha-C-**aminoalkylthymidines** form thermally stable duplexes with DNA and RNA. A candidate for potent antisense molecules
AUTHOR: Kanazaki M; Ueno Y; Shuto S; Matsuda A (Reprint)
CORPORATE SOURCE: HOKKAIDO UNIV, GRAD SCH PHARMACEUT SCI, KITA KU, KITA 12, NISHI 6, SAPPORO, HOKKAIDO 060081, JAPAN (Reprint); HOKKAIDO UNIV, GRAD SCH PHARMACEUT SCI, KITA KU, SAPPORO, HOKKAIDO 060081, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, (22 MAR 2000) Vol. 122, No. 11, pp. 2422-2432. Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036. ISSN: 0002-7863.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: PHYS; LIFE
LANGUAGE: English
REFERENCE COUNT: 64

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The properties of phosphodiester oligodeoxynucleotides (ODNs) containing 4'alpha-C-**aminomethyl**, -ethyl, -propyl, and -N-(2-**aminoethyl**)carbamoylthymidines (1, 2, 4, and 5) as potential antisense molecules are investigated in detail. We developed new radical chemistry with a vinylsilyl or an allylsilyl;I group as a temporary radical acceptor tether to synthesize the required 4'alpha-branched thymidines. Thus, an intramolecular radical cyclization of 4'-phenylseleno nucleosides 7a and 7b, which have a dimethylvinylsilyl and a dimethylallylsilyl group at the 3'-hydroxyl, respectively, with Bu3SnH/AIBN and subsequent Tamao oxidation provided 5'-O-[dimethoxytrityl(DMTr)]-4'alpha-C-(2-hydroxyethyl)thymidine (8a) and 5'-O-DMTr-4'alpha-C-(3-hydroxypropyl)thymidine (8b). Compounds 8a and 8b were then converted into 4'alpha-C-(2-trifluoroacetamidoethyl)thymidine 12a and 4'alpha-C-(3-trifluoroacetamidopropyl)thymid 12b, which were phosphitylated to give the phosphoramidite units 14a and 14b. The phosphoramidite units of 1 and 5 were prepared by previous methods. The nucleosides 1, 2, 1, and 5 were incorporated into the 18-mer, 5'-d[MTMTMTMTMTMTMTMTMT]-3' where M is 5-methyl-2'-deoxycytidine, instead of T at various positions. We also prepared a 21-mer ODN 29 with a mixed sequence containing five residues of **2**. The ODNs containing the **modified** nucleosides formed more stable duplexes with complementary DNA than the corresponding unmodified ODN. These ODNs also formed stable duplexes with the complimentary RNA, The ODNs containing the modified **nucleosides** were significantly **resistant** to **nucleolytic** hydrolysis by both snake venom phosphodiesterase (a 3'-exonuclease) and DNase 1 (an endonuclease) and were also very stable in PBS containing 50% human serum. It is worthwhile to note that these ODNs contain natural phosphodiester linkages. Furthermore, the duplexes formed

by the ODNs containing the modified nucleosides and their complementary RNAs were good substrates for Escherichia coil RNase H and HeLa cell nuclear extracts as a source of human RNase H. Thus. these ODNs were identified as candidates for antisense molecules.

L14 ANSWER 24 OF 67 MEDLINE
ACCESSION NUMBER: 2001034055 MEDLINE
DOCUMENT NUMBER: 20527459 PubMed ID: 11078022
TITLE: Synthetic **oligonucleotides** as RNA mimetics: **2'-modified** Rnas and N3'-->P5' phosphoramidates.
AUTHOR: Egli M; Gryaznov S M
CORPORATE SOURCE: Department of Molecular Pharmacology and Biological Chemistry, Northwestern University Medical School, Chicago, Illinois 60611, USA.
SOURCE: CELLULAR AND MOLECULAR LIFE SCIENCES, (2000 Sep) 57 (10) 1440-56. Ref: 84
Journal code: 9705402. ISSN: 1420-682X.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001130

AB Significant interest in synthetic DNA and RNA **oligonucleotides** and their analogues has marked the past two decades of research in chemistry and biochemistry. This attention was largely determined by the great potential of these compounds for various therapeutic applications such as **antisense**, antigene and ribozyme-based agents. **Modified oligonucleotides** have also become powerful molecular biological and biochemical research tools that allow fast and efficient regulation of gene expression and gene functions in vitro and in vivo. These applications in turn are based on the ability of the **oligonucleotides** to form highly sequence-specific complexes with **nucleic acid** targets of interest. This review summarizes recent advances in the design, synthesis, biochemical and structural properties of various RNA analogues. These comprise 3'-**modified oligonucleotide** N3'-->P5' phosphoramidates, analogues with **modifications** at the **2'**-position of nucleoside sugar rings, or combinations of the two. Among the properties of the RNA minetics reviewed here are the thermal stability of their duplexes and triplexes, hydrolytic **resistance** to cellular **nucleases** and biological activity in in vitro and in vivo systems. In addition, key structural aspects of the complexes formed by the RNA analogues, including interaction with water molecules and ions, are analyzed and presented.

L14 ANSWER 25 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 132:20490 CA
TITLE: Improving **nuclease resistance** of ribozymes for therapeutic use by **amino** modification of pyrimidine residues
INVENTOR(S): Sioud, Mouldy
PATENT ASSIGNEE(S): The Norwegian Radium Hospital Research Foundation, Norway; Dzieglewska, Hanna Eva
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9963066	A2	19991209	WO 1999-GB1706	19990528
WO 9963066	A3	20011011		
W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2329247	AA	19991209	CA 1999-2329247	19990528
AU 9941557	A1	19991220	AU 1999-41557	19990528
AU 750190	B2	20020711		
EP 1144599	A2	20011017	EP 1999-925169	19990528
EP 1144599	A3	20020206		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
NO 2000006072	A	20010123	NO 2000-6072	20001130
US 2003045486	A1	20030306	US 2000-725926	20001130

PRIORITY APPLN. INFO.: GB 1998-11750 A 19980601
WO 1999-GB1706 W 19990528

AB A method of improving the stability of ribozymes for therapeutic use against nucleases by **amino** modification of pyrimidines is described. A typical modification includes three or more pyrimidine nucleotides **modified** at the **2**'-position to **2**'-**amino** pyrimidine nucleotides leading to improved stability to RNAse degrdn. and .gtoreq.85% of the catalytic activity of the unmodified ribozyme. The prepn. of ribozymes contg. 2'-**amino**-2'-deoxyuridine and 2'-**amino**-2'-deoxycytidine by transcription of ribozyme minigenes with T7 polymerase is demonstrated. The catalytic activity of a ribozyme against tumor necrosis factor .alpha. mRNA was unaffected by 2'-**amino** substitution. The serum half life of an unmodified ribozyme in mouse was 0.3 min. and for the modified form it was >65h. Modified and unmodified ribozymes were effective in degrading protein kinase C mRNA in cultured glioma cells and in lowering the levels of other glioma-assocd. gene products and also led to apoptosis. In vivo, the ribozymes had similar effects on glioma cells inoculated into BDIX rats. Hammerhead ribozymes were also largely unaffected as long as bases involved in Mg2+ were not substituted. The effect could be reversed by substitution of Mg2+ with Mn2+.

L14 ANSWER 26 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 130:163953 CA
TITLE: **Nuclease resistance** of 2'-O-methyl **oligoribonucleotides** and their preparation and use as hybridization probes
INVENTOR(S): Callaghan, Kay; Theaker, Jane
PATENT ASSIGNEE(S): Zeneca Limited, UK
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9905314	A1	19990204	WO 1998-GB2176	19980721
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 998584	A1	20000510	EP 1998-935182	19980721
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001511357	T2	20010814	JP 2000-504281	19980721
US 2002102571	A1	20020801	US 2001-883489	20010619

PRIORITY APPLN. INFO.:

GB 1997-15522	A	19970724
WO 1998-GB2176	W	19980721
US 2000-463324	B1	20000124

AB **Oligoribonucleotides modified** by **2**'-O-methylation are **resistant** to **nuclease** digestion and can be used for in situ **nucleic acid** hybridization, esp. with "Mol. Beacon" probes that fluoresce upon hybridization. **Oligonucleotides** may be **modified** using other lower **alkyl** groups on the 2'-OH. The hybridization and fluorescence properties of Mol. Beacons with a 2'-O-Me ribose are characterized. Use of 2'-O-Me probes to detect wild-type and mutant alleles in the gene assocd. with hereditary hemochromatosis is demonstrated.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 27 OF 67 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 131:237986 CA

TITLE: Gapped 2'-**alkyl** or 2-deoxy-erythro-pentofuranosyl or other **2'-modified oligonucleotides** for **antisense** therapy

INVENTOR(S): Cook, Phillip Dan; Monia, Brett P.

PATENT ASSIGNEE(S): Isis Pharmaceuticals Inc., USA

SOURCE: U.S., 34 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 100

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5955589	A	19990921	US 1995-465880	19950606
AU 713740	B2	19991209	AU 1997-26244	19970624
AU 9726244	A1	19971106		
US 6232463	B1	20010515	US 1998-128508	19980804
US 6399754	B1	20020604	US 1998-135202	19980817

PRIORITY APPLN. INFO.:

US 1991-814961	B2	19911224
WO 1992-US11339	B2	19921223
AU 1993-38025	A3	19930225
US 1994-244993	A2	19940621
US 1995-465880	A2	19950606
US 1995-471973	A3	19950606
US 1997-948151	A1	19971009

AB **Oligonucleotides** and other macromols. are provided which have increased **nuclease resistance**, substituent groups for increasing binding affinity to complementary strand, and subsequences of 2'-deoxy-erythro-pentofuranosyl nucleotides that activate RNase H. Such **oligonucleotides** and macromols. are useful for diagnostics and other research purposes, for modulating the expression of a protein in organisms, and for the diagnosis, detection and treatment of other conditions susceptible to **oligonucleotide** therapeutics. For the

purpose of illustration, the **antisense oligonucleotides** of the invention are used in a H-ras-luciferase expression system, to hybridize with **nucleic acids** related to protein kinase C-.alpha., to inhibit c-raf expression, and as antiviral agents.

REFERENCE COUNT: 117 THERE ARE 117 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 28 OF 67 MEDLINE

ACCESSION NUMBER: 2000056229 MEDLINE
DOCUMENT NUMBER: 20056229 PubMed ID: 10588690
TITLE: Structural origins of the exonuclease resistance of a zwitterionic RNA.
AUTHOR: Teplova M; Wallace S T; Tereshko V; Minasov G; Symons A M; Cook P D; Manoharan M; Egli M
CORPORATE SOURCE: Department of Molecular Pharmacology, The Drug Discovery Program, Northwestern University Medical School, Chicago, IL 60611-3008, USA.
CONTRACT NUMBER: RO1 GM-55237 (NIGMS)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Dec 7) 96 (25) 14240-5. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1D8Y; PDB-1D9D; PDB-1D9H; +
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000114
Last Updated on STN: 20000114
Entered Medline: 20000105

AB **Nuclease resistance** and RNA affinity are key criteria in the search for optimal **antisense nucleic acid modifications**, but the origins of the various levels of **resistance** to **nuclease degradation** conferred by chemical **modification** of DNA and RNA are currently not understood. The **2'-O-aminopropyl** (AP)-RNA **modification** displays the highest **nuclease resistance** among all phosphodiester-based analogues and its RNA binding affinity surpasses that of phosphorothioate DNA by 1 degrees C per **modified** residue. We found that **oligodeoxynucleotides** containing AP-RNA residues at their 3' ends competitively inhibit the degradation of single-stranded DNA by the Escherichia coli Klenow fragment (KF) 3'-5' exonuclease and snake venom phosphodiesterase. To shed light on the origins of **nuclease resistance** brought about by the AP **modification**, we determined the crystal structure of an A-form DNA duplex with AP-RNA **modifications** at 1.6-A resolution. In addition, the crystal structures of complexes between short DNA fragments carrying AP-RNA **modifications** and wild-type KF were determined at resolutions between 2.2 and 3.0 A and compared with the structure of the complex between **oligo**(dT) and the D355A/E357A KF mutant. The structural models suggest that interference of the positively charged 2'-O-substituent with the metal ion binding site B of the exonuclease allows AP-RNA to effectively slow down degradation.

L14 ANSWER 29 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5

ACCESSION NUMBER: 1999:492185 BIOSIS
DOCUMENT NUMBER: PREV199900492185
TITLE: Synthesis, hybridization, and **nuclease resistance** properties of **2'-O-aminooxyethyl modified**

oligonucleotides.

AUTHOR(S): Kawasaki, Andrew M. (1); Casper, Martin D.; Prakash, Thazha P.; Manalili, Sheri; Sasmor, Henri; Manoharan, Muthiah; Cook, P. Dan

CORPORATE SOURCE: (1) Medicinal Chemistry, ISIS Pharmaceuticals, 2292 Faraday Ave., Carlsbad, CA, 92008 USA

SOURCE: Nucleosides & Nucleotides, (June July, 1999) Vol. 18, No. 6-7, pp. 1419-1420.
ISSN: 0732-8311.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB We have synthesized the novel 2'-O-AOE- and MIOE-5-methyluridine and -adenosine nucleosides and successfully incorporated them into **oligonucleotides**. The **2'-O-modifications** significantly enhance hybridization against RNA (1.2 deg C/substitution) and furthermore, exhibits specificity for RNA vs. DNA. The **nuclease resistance** (SVPD) of **2'-O-AOE** and MIOE **modified oligonucleotides** is comparable to that of 2'-O-MOE.

L14 ANSWER 30 OF 67 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 131:243519 CA

TITLE: 2'-DMAOE RNA: Emerging oligonucleotides with promising antisense properties

AUTHOR(S): Prakash, Thazha P.; Kawasaki, Andrew M.; Vasquez, Guillermo; Fraser, Allister S.; Casper, Martin D.; Cook, P. Dan; Manoharan, Muthiah

CORPORATE SOURCE: Department of Medicinal Chemistry, Isis Pharmaceuticals, Carlsbad, CA, 92008, USA

SOURCE: Nucleosides & Nucleotides (1999), 18(6 & 7), 1381-1382
CODEN: NUNUD5; ISSN: 0732-8311

PUBLISHER: Marcel Dekker, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A symposium on the design of the **2'-O-(aminooxyethyl) modification** (**2'-AOE**) and **2'-O-(dimethylaminooxyethyl) modification** (**2'-DMAOE**) and the synthesis of **oligomers** with these **modifications**. 2'-DMAOE oligomers demonstrate higher binding affinity and **nuclease resistance** than 2'-MOE oligomers and stand out as promising candidates for future antisense oligonucleotide drug development.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 31 OF 67 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 131:332551 CA

TITLE: VEGF165 mediates glomerular endothelial repair

AUTHOR(S): Ostendorf, Tammo; Kunter, Uta; Eitner, Frank; Loos, Anneke; Regele, Heinz; Kerjaschki, Dontscho; Henninger, Dwight D.; Janjic, Nebojsa; Floege, Jurgen

CORPORATE SOURCE: Division of Nephrology, Medizinische Hochschule, Hannover, 30623, Germany

SOURCE: Journal of Clinical Investigation (1999), 104(7), 913-923
CODEN: JCINAO; ISSN: 0021-9738

PUBLISHER: American Society for Clinical Investigation

DOCUMENT TYPE: Journal

LANGUAGE: English

AB VEGF165, the most abundant isoform in man, is an angiogenic cytokine that also regulates vascular permeability. Its function in the renal

glomerulus, where it is expressed in visceral epithelial and mesangial cells, is unknown. To assess the role of VEGF165 in glomerular disease, the authors administered a novel antagonist - a high-affinity, **nuclease-resistant** RNA aptamer coupled to 40-kDa polyethylene glycol (PEG) - to normal rats and to rats with mesangioproliferative nephritis, passive Heymann nephritis (PHN), or puromycin **aminonucleoside** nephrosis (PAN). In normal rats, antagonism of VEGF165 for 21 days failed to induce glomerular pathol. or proteinuria. In rats with mesangioproliferative nephritis, the VEGF165 aptamer (but not a sequence-scrambled control RNA or PEG alone) led to a redn. of glomerular endothelial regeneration and an increase in endothelial cell death, provoking an 8-fold increase in the frequency of glomerular microaneurysms by day 6. In contrast, early leukocyte influx and the proliferation, activation, and matrix accumulation of mesangial cells were not affected in these rats. In rats with PHN or PAN, administration of the VEGF165 aptamer did not influence the course of proteinuria using various dosages and administration routes. These data identify VEGF165 as a factor of central importance for endothelial cell survival and repair in glomerular disease, and point to a potentially novel way to influence the course of glomerular diseases characterized by endothelial cell damage, such as various glomerulonephritides, thrombotic microangiopathies, or renal transplant rejection.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 32 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6

ACCESSION NUMBER: 1999:118350 BIOSIS
DOCUMENT NUMBER: PREV199900118350
TITLE: Synthesis, hybridization and **nuclease resistance** properties of **2'-O-aminooxyethyl** (2'-O-AOE) **modified oligonucleotides.**
AUTHOR(S): Kawasaki, Andrew M. (1); Casper, Martin D.; Prakash, Thazha P.; Manalili, Sheri; Sasmor, Henri; Manoharan, Muthiah; Cook, P. Dan
CORPORATE SOURCE: (1) Dep. Med. Chem., Isis Pharm., 2292 Faraday Ave., Carlsbad, CA 92008 USA
SOURCE: Tetrahedron Letters, (Jan. 22, 1999) Vol. 40, No. 4, pp. 661-664.
ISSN: 0040-4039.
DOCUMENT TYPE: Article
LANGUAGE: English

AB The novel RNA mimic 2'-O-AOE has been incorporated into antisense **oligonucleotides**. This **2'-O-modification** significantly enhances hybridization against target RNA, and furthermore, exhibits specificity for RNA over DNA. The **nuclease resistance** (SVPD) of **2'-O-AOE modified** phosphodiester **oligonucleotides** is significantly higher than the unmodified DNA and comparable to the 2'-O-MOE oligonucleotides.

L14 ANSWER 33 OF 67 MEDLINE

ACCESSION NUMBER: 1999177085 MEDLINE
DOCUMENT NUMBER: 99177085 PubMed ID: 10077480
TITLE: Duplex recognition by **oligonucleotides** containing 2'-deoxy-2'-fluoro-D-arabinose and 2'-deoxy-2'-fluoro-D-ribose. Intermolecular 2'-OH-phosphate contacts versus sugar puckering in the stabilization of triple-helical complexes.
AUTHOR: Wilds C J; Damha M J
CORPORATE SOURCE: Department of Chemistry, Otto Maass Chemistry Building, McGill University, 801 Sherbrooke Street West, Montreal,

Quebec, Canada H3A 2K6.
SOURCE: BIOCONJUGATE CHEMISTRY, (1999 Mar-Apr) 10 (2) 299-305.
Journal code: 9010319. ISSN: 1043-1802.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511
Last Updated on STN: 19990511
Entered Medline: 19990429

AB To gain insight into the origins of the large binding affinity of RNA toward target duplexes, 2'-deoxy-2'-**fluororibonucleic acid** (2'F-RNA) and 2'-deoxy-2'-**fluoroarabinonucleic acid** (2'F-ANA) were tested for their ability to recognize duplex DNA, duplex RNA, and RNA-DNA hybrids. 2'F-RNA, 2'F-ANA, and the corresponding control single-stranded (ss) DNA strands were shown to form triple-helical complexes only with duplex DNA and hybrid DNA (Pu)-RNA (Py), but not with duplex RNA and hybrid RNA (Pu)-DNA (Py). In contrast, an RNA third strand recognized all four possible duplexes (DD, DR, RD, and RR) as previously demonstrated by Roberts and Crothers [(1992) Science 258, 1463-1466]. The 2'F-RNA (C3'-endo) strand exhibited significantly reduced affinity for duplexes compared to an unmodified RNA (C3'-endo) strand. These findings are consistent with the intermolecular 2'-OH-phosphate contact mechanism proposed by Escude et al. [(1993) **Nucleic Acids** Res. 24, 5547-5553], as a ribo 2'-F atom should not interact with a negatively charged phosphate. In addition, they emphasize the role of the 2'-OH ribose as a general recognition and binding determinant of RNA. The **2'-F arabino modification** (2'F-ANA, C2'-endo) led to a considerable increase in the binding affinity for duplex DNA, as compared to those of DNA and 2'F-RNA third strands. This is likely to be the result of a greater population of C2'-endo pucker of the 2'F-ANA compared to DNA. The enhancement observed for 2'F-ANA strands toward duplex DNA is comparable to that observed with 2'-OMe RNA. Since 2'F-ANA has been shown to be more **resistant** to **nuclease degradation** than DNA, these results are likely to stimulate experimental work on arabinose derivatives in laboratories concerned with targeting DNA sequences in vivo ("antigene" strategy).

L14 ANSWER 34 OF 67 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 1999:403172 SCISEARCH
THE GENUINE ARTICLE: 197WC
TITLE: Inhibition of translation of hepatitis C virus RNA by **2'-modified antisense oligonucleotides**
AUTHOR: BrownDriver V (Reprint); Eto T; Lesnik E; Anderson K P; Hanecak R C
CORPORATE SOURCE: ISIS PHARMACEUT, 2280 FARADAY AVE, CARLSBAD, CA 92008 (Reprint); CHEMOSEROTHERAPEUT RES INST, KUMAMOTO 86912, JAPAN
COUNTRY OF AUTHOR: USA; JAPAN
SOURCE: ANTISENSE & NUCLEIC ACID DRUG DEVELOPMENT, (APR 1999) Vol. 9, No. 2, pp. 145-154.
Publisher: MARY ANN LIEBERT INC PUBL, 2 MADISON AVENUE, LARCHMONT, NY 10538.
ISSN: 1087-2906.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 50

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Inhibition of hepatitis C virus (HCV) gene expression by antisense oligonucleotides was investigated using both a rabbit reticulocyte lysate in vitro translation assay and a transformed human hepatocyte cell expression assay. Screening of overlapping oligonuceeotides complementary to the HCV 5' noncoding region and the core open reading frame (ORF) identified a region susceptible to translation inhibition between nucleotides 335 and 379, Comparison of 2'-deoxy-, 2'-O-methyl-, 2'-O-methoxyethyl-, **2'-O-propyl-**, and **2'-fluoro-modified** phosphodiester **oligoribonucleotides** demonstrated that increased translation inhibition correlated with both increased binding affinity and nuclease stability, In cell culture assays, **2'-O-methoxyethyl-modified oligonucleotides** inhibited HCV core protein synthesis with comparable potency to phosphorothioate oligodeoxynucleotides. Inhibition of HCV core protein expression by **2'-modified oligonucleotides** occurred by an RNase H-independent translational arrest mechanism.

L14 ANSWER 35 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 132:134188 CA
TITLE: Aptamers as tools in molecular biology and immunology
AUTHOR(S): Famulok, M.; Mayer, G.
CORPORATE SOURCE: Institut fur Organische Chemie and Biochemie, Bonn, D-53121, Germany
SOURCE: Current Topics in Microbiology and Immunology (1999), 243(Combinatorial Chemistry in Biology), 123-136
CODEN: CTMIA3; ISSN: 0070-217X
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 74 refs. In 1990, the first RNA aptamer for bacteriophage T4 DNA polymerase was introduced, obtained by a new combinatorial technique designated as SELEX (systematic evolution of ligands by exponential enrichment). In parallel; it was shown that it is also possible to select RNA aptamers which are able to specifically complex org. mols. of low mol. wt., thus serving as receptor mols. based on **nucleic acids** rather than proteins. Since then, considerable progress has been achieved in the field of in vitro selection of combinatorial **nucleic acid** libraries, which demonstrates its impressive potential as a tool in mol. biol., diagnostics, mol. medicine, drug discovery, and bio-org. chem. Today, the SELEX process has been applied to more than a hundred different target mols., and aptamers are known for almost every kind of targets such as org. dyes, amino acids, biol. cofactors, antibiotics, peptides and proteins or even whole viruses, showing that aptamers can be obtained for almost any desired target whether complex or small. The isolation of specific antagonists for proteins which are involved in disease processes is one of the major goals in pharmacol. research. Drug discovery has been greatly facilitated by computer-assisted drug design and various screening strategies of diverse combinatorial libraries of small mols., peptides, Fab fragments, and antibodies. The SELEX technol. provides a powerful method for the screening of large libraries of **oligonucleotides**, with diversities of up to 1015 different mols., for specific ligand-binding **nucleic acids** which in many cases have been shown to not only bind a certain target protein, but also to inhibit its biol. function. Many isolated aptamers are aimed at possible therapeutic and/or diagnostic applications. Insufficient stability, often cited as the major potential drawback of **nucleic acids** as therapeutic agents, can easily be overcome by using libraries of chem. **modified nucleic acids**, such as **2'-fluoro-** or 2'-amino-2'-deoxypyrimidine contg. **nucleic acids**. **Modifications** of that kind have been shown to be

compatible with the enzymic steps of the SELEX process. Other strategies which circumvent the stability problem of RNA or DNA include the so-called mirror-image, or Spiegelmer, approach by exploiting **nuclease resistance** of the enantiomer of naturally occurring **nucleic acids**. Various recent examples illustrate the potential of aptamers in affecting cellular processes. Here, an overview is given on recent progress in **oligonucleotide** selections and applications of aptamers as potential tools in drug discovery, diagnostics, mol. medicine, and for the dissection of cellular processes of immunol. relevance.

REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 36 OF 67 MEDLINE
ACCESSION NUMBER: 2000265282 MEDLINE
DOCUMENT NUMBER: 20265282 PubMed ID: 10807002
TITLE: **2'**-carbohydrate **modifications** in **antisense oligonucleotide** therapy: importance of conformation, configuration and conjugation.
AUTHOR: Manoharan M
CORPORATE SOURCE: Department of Medicinal Chemistry, Isis Pharmaceuticals, Carlsbad, CA 92008, USA.. mmanohar@isisph.com
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA, (1999 Dec 10) 1489 (1) 117-30. Ref: 72
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000606
Last Updated on STN: 20000606
Entered Medline: 20000524

AB The 2'-position of the carbohydrate moiety has proven to be a fertile position for **oligonucleotide modifications** for **antisense** technology. The **2'-modifications** exhibit high binding affinity to target RNA, enhanced chemical stability and **nuclease resistance** and increased lipophilicity. All high binding affinity **2'-modifications** have C3'-endo sugar pucker. In addition to gauche effects, charge effects are also important in determining the level of their **nuclease resistance**. Pharmacokinetic properties of **oligonucleotides** are altered by **2'**-conjugates. For certain **modifications** (e.g., **2'**-F), the configuration at the 2'-position, arabino vs. ribo, determines their ability to activate the enzyme RNase H.

L14 ANSWER 37 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 128:279586 CA
TITLE: Reagents and methods for modulating gene expression through RNA mimicry
INVENTOR(S): Ecker, David J.; Bruice, Thomas W.; Vickers, Timothy A.
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: U.S., 27 pp., Cont.-in-part of U.S. Ser. No. 497,090, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5736294	A	19980407	US 1991-724500	19910627
CA 2078659	AA	19910922	CA 1991-2078659	19910319
HU 62658	A2	19930528	HU 1992-3010	19910319
US 5874564	A	19990223	US 1995-461418	19950605

PRIORITY APPLN. INFO.: US 1990-497090 B2 19900321
US 1992-927505 B1 19920916

AB Expression of genes may be modulated by employment of compns. which are capable of RNA mimicry. A portion of RNA coded by the gene whose expression is to be modulated is selected which is capable of interacting with one or more proteins. An oligonucleotide or oligonucleotide analog is then prepd. in such a way as to mimic the portion of the RNA. Cells contg. the gene are then contacted with the oligonucleotide or oligonucleotide analog to effect the modulation. Therapeutic compns. and methods, esp. for the treatment of human immunodeficiency, are disclosed in which oligonucleotide mimics of the TAR element interfere with binding of the TAR element to Tat protein and thus inhibit HIV replication. The **oligonucleotide** mimics are **modified** with **2** '-O-Me groups or within the pyrimidine moiety (5-**bromouridine**, 6-azauridine, etc.) for improved **nuclease resistance** within the cell.

L14 ANSWER 38 OF 67 MEDLINE
ACCESSION NUMBER: 1998367504 MEDLINE
DOCUMENT NUMBER: 98367504 PubMed ID: 9692952
TITLE: Correlating structure and stability of DNA duplexes with incorporated **2'-O-modified** RNA analogues.
AUTHOR: Tereshko V; Portmann S; Tay E C; Martin P; Natt F; Altmann K H; Egli M
CORPORATE SOURCE: Drug Discovery Program, Northwestern University Medical School, Chicago, Illinois 60611-3008, USA.
CONTRACT NUMBER: R01 GM-55237 (NIGMS)
SOURCE: BIOCHEMISTRY, (1998 Jul 28) 37 (30) 10626-34.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980903
Last Updated on STN: 19980903
Entered Medline: 19980821

AB Chemically **modified nucleic acids** are currently being evaluated as potential **antisense** compounds for therapeutic applications. 2'-O-Ethylene glycol substituted **oligoribonucleotides** are second-generation **antisense** inhibitors of gene expression with promising features for in vivo use. Relative to DNA, they display improved RNA affinity and higher **nuclease resistance**. Moreover, chimeric **oligonucleotides** with 2'-O-methoxyethyl ribonucleoside wings and a central DNA phosphorothioate window have been shown to effectively reduce the growth of tumors in animal models at low doses. Using X-ray crystallography, we have determined the structures of three A-form DNA duplexes containing the following **2'-O-modified** ribothymidine building blocks: **2'-O**-methoxyethyl ribo-T, 2'-O-methyl[tri(oxyethyl)] ribo-T, and 2'-O-ethoxymethylene ribo-T. In contrast to 2'-O-ethylene glycol substituents, the presence of a 2'-O-ethoxymethylene group leads to slightly reduced RNA affinity of the corresponding **oligonucleotides**. The three structures allow a

qualitative rationalization of the differing stabilities of duplexes between **oligonucleotides** comprising these types of **2'-O-modified** ribonucleotides and complementary RNAs. The stabilizing 2'-O-ethylene glycol substituents are conformationally preorganized for the duplex state. Thus, the presence of one or several ethylene glycol moieties may reduce the conformational space of the substituents in an **oligonucleotide** single strand. In addition, most of these preferred conformations appear to be compatible with the minor groove topology in an A-type duplex. Factors that contribute to the conformational rigidity of the 2'-O-substituents are anomeric and gauche effects, electrostatic interactions between backbone and substituent, and bound water molecules.

L14 ANSWER 39 OF 67 MEDLINE
ACCESSION NUMBER: 1998223642 MEDLINE
DOCUMENT NUMBER: 98223642 PubMed ID: 9554886
TITLE: **Nuclease-resistant** composite 2',5'-**oligoadenylate**-3', 5'-**oligonucleotides** for the targeted destruction of RNA: 2-5A-iso-**antisense**.
AUTHOR: Xiao W; Li G; Player M R; Maitra R K; Waller C F; Silverman R H; Torrence P F
CORPORATE SOURCE: Section on Biomedical Chemistry, Laboratory of Medicinal Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA.
CONTRACT NUMBER: 1 PO1 CA 62220 (NCI)
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (1998 Apr 23) 41 (9) 1531-9.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980529
Last Updated on STN: 19980529
Entered Medline: 19980521

AB A new **modification** of **2**-5A-**antisense**, **2**-5A-iso-**antisense**, has been developed based on a reversal of the direction of the polarity of the **antisense** domain of a 2-5A-**antisense** composite **nucleic acid**. This **modification** was able to anneal with its target RNA as well as the parental 2-5A-**antisense** chimera. The 2-5A-iso-**antisense** **oligonucleotide** displayed enhanced **resistance** to **degradation** by 3'-exonuclease enzyme activity such as that represented by snake venom phosphodiesterase and by that found in human serum. 2-5A-Iso-**antisense** was able to effect the degradation of a synthetic nontargeted substrate, [5'-32P]pC11U2C7, and two targeted RNAs, PKR and BCR mRNAs, in a cell-free system containing purified recombinant human 2-5A-dependent RNase L. These results demonstrated that the novel structural **modification** represented by **2**-5A-iso-**antisense** provided a stabilized biologically active formulation of the 2-5A-**antisense** strategy.

L14 ANSWER 40 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 127:229652 CA
TITLE: Sugar-**modified** gapped **oligonucleotides** for induction of mRNA degradation by RNase H
INVENTOR(S): Cook, Phillip D.; Monia, Brett; Altmann, Karl-Heinz; Martin, Pierre

PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA; Novartis A.-G.; Cook, Phillip D.; Monia, Brett; Altmann, Karl-Heinz; Martin, Pierre
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9730067	A1	19970821	WO 1997-US2043	19970207
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2246229	AA	19970821	CA 1997-2246229	19970207
AU 9719552	A1	19970902	AU 1997-19552	19970207
AU 725262	B2	20001012		
EP 882061	A1	19981209	EP 1997-907581	19970207
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO				
CN 1214688	A	19990421	CN 1997-193129	19970207
BR 9707529	A	20000104	BR 1997-7529	19970207
NZ 331217	A	20000228	NZ 1997-331217	19970207
JP 2000504725	T2	20000418	JP 1997-529412	19970207
US 6451991	B1	20020917	US 1997-802331	19970211
ZA 9701208	A	19971023	ZA 1997-1208	19970213
NO 9803718	A	19981013	NO 1998-3718	19980813

PRIORITY APPLN. INFO.: US 1996-11620P P 19960214
WO 1997-US2043 W 19970207

AB This invention is directed to the synthesis and use of **oligonucleotides** for eliciting RNase H activity for strand cleavage in an opposing strand. Included in the invention are **oligonucleotides** wherein at least some of the nucleoside units of the **oligonucleotides** are functionalized to be **nuclease resistant**, at least some of the nucleoside units of the **oligonucleotides** include a substituent that potentiates hybridization of the **oligonucleotide** to a **complementary** strand of **nucleic acid**, and at least some of the nucleoside units of the **oligonucleotides** include 2'-deoxy-erythro-pentofuranosyl sugar moieties. The 2'-methoxyethoxy functionalization increase **nuclease resistance** and potentiates hybridization. **Oligonucleotides** contg. 2'-methoxyethoxy and 2'-deoxy residues and mixts. of phosphodiester and phosphorothioate linkages targeted to PKC .alpha. mRNA or c-raf mRNA were prepd. Both types of **oligonucleotides** inhibited prodn. of mRNA in vitro; both inhibited tumor growth in vivo. Other **oligonucleotides** contg. 2'-O-Me, 2'-O-Pr and 2'-deoxy-2'-**fluororibosyl**-contg. residues were prepd. and demonstrated activity in vitro and in vivo.

L14 ANSWER 41 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 127:1627 CA
TITLE: Gapped 2'-O-methyl or 2'-deoxy-erythro-pentofuranosyl or other **2'-modified** **oligonucleotides** that activate RNase H for

disease diagnosis or **antisense** therapy

INVENTOR(S): Cook, Phillip D.; Monia, Brett P.

PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA

SOURCE: U.S., 23 pp., Cont.-in-part of U.S. Ser. No. 814,961, abandoned.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 100

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5623065	A	19970422	US 1994-244993	19940621
CA 2089376	AA	19920214	CA 1991-2089376	19910812
WO 9313121	A1	19930708	WO 1992-US11339	19921223
W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
EP 1044987	A2	20001018	EP 2000-202252	19921223
EP 1044987	A3	20011004		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
JP 2001002696	A2	20010109	JP 2000-143468	19921223
JP 08098700	A2	19960416	JP 1995-175173	19950711
US 5856455	A	19990105	US 1997-861306	19970421
US 5965722	A	19991012	US 1997-848840	19970430
AU 713740	B2	19991209	AU 1997-26244	19970624
AU 9726244	A1	19971106		
US 6232463	B1	20010515	US 1998-128508	19980804
US 6399754	B1	20020604	US 1998-135202	19980817
US 6326199	B1	20011204	US 1999-453514	19991201
US 2001044145	A1	20011122	US 2001-799848	20010305
US 2003004325	A1	20030102	US 2001-996263	20011128

PRIORITY APPLN. INFO.:

US 1990-566977	B2	19900813
US 1991-814961	B2	19911224
WO 1992-US11339	W	19921223
US 1990-463358	B2	19900111
WO 1991-US243	W	19910111
WO 1991-US5720	W	19910812
US 1991-801168	B1	19911120
US 1992-835932	A2	19920305
US 1992-854634	B2	19920701
US 1992-958134	B2	19921005
EP 1993-902851	A3	19921223
JP 1993-511953	A3	19921223
US 1993-7996	B2	19930121
AU 1993-38025	A3	19930225
US 1993-39979	B1	19930330
US 1993-40526	A2	19930331
US 1993-40903	A3	19930331
US 1993-40933	B1	19930331
WO 1993-US9346	B1	19931001
US 1994-227180	A2	19940413
US 1994-244993	A3	19940621
US 1994-300072	A3	19940902
US 1994-317289	A2	19941003
US 1994-335046	A2	19941107
US 1995-411734	A2	19950403
US 1995-465866	A2	19950606
US 1995-465880	A2	19950606
US 1995-468037	A2	19950606

US 1995-471973	A3	19950606
US 1995-488256	A2	19950607
US 1997-794493	A2	19970204
US 1997-861306	A3	19970421
US 1997-948151	A1	19971009
US 1997-67458P	P	19971204
WO 1998-US13966	W	19980706
US 1998-135202	A1	19980817
US 1998-144611	A3	19980831
US 1998-203716	A1	19981202
US 1999-343809	B1	19990630
US 1999-453514	A2	19991201
US 2000-462280	A2	20000301
US 2000-684254	A2	20001006
US 2001-781712	A2	20010212

AB **Oligonucleotides** and other macromols. are provided that have increased **nuclease resistance**, substituent groups for increasing binding affinity to complementary strand, and subsequences of 2'-deoxy-erythro-pentofuranosyl nucleotides that activate RNase H enzyme. Such **oligonucleotides** and macromols. are useful for diagnostics and other research purposes, for modulating protein in organisms, and for the diagnosis, detection and treatment of other conditions susceptible to **antisense** therapeutics.

L14 ANSWER 42 OF 67 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 97:430751 SCISEARCH
THE GENUINE ARTICLE: XB627
TITLE: Nucleosides and nucleotides .160. Synthesis of oligodeoxyribonucleotides containing 5-(N-**aminoalkyl**)carbamoyl-**2**'-deoxyuridin by a new postsynthetic **modification** method and their thermal stability and **nuclease**-**resistance** properties
AUTHOR: Haginoya N; Ono A; Nomura Y; Ueno Y; Matsuda A (Reprint)
CORPORATE SOURCE: HOKKAIDO UNIV, FAC PHARMACEUT SCI, KITA KU, KITA-12, NISHI-6, SAPPORO, HOKKAIDO 060, JAPAN (Reprint); HOKKAIDO UNIV, FAC PHARMACEUT SCI, KITA KU, SAPPORO, HOKKAIDO 060, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: BIOCONJUGATE CHEMISTRY, (MAY-JUN 1997) Vol. 8, No. 3, pp. 271-280.
Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036.
ISSN: 1043-1802.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 40

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Heptadecadeoxynucleotides containing 5-(N-**aminoethyl**- or N-**aminohexyl**)carbamoyl-2'-deoxyuridines (E or H) were synthesized using a newly developed postsynthetic modification method. As a convertible nucleoside unit, 5-methoxycarbonyl-2'-deoxyuridine (1) was initially incorporated into oligodeoxynucleotides (ODNs) according to the phosphoramidite method at various positions using a DNA synthesizer. Fully protected ODNs attached to a solid support were treated with **alkyldiamines** such as ethylenediamine and 1,6-hexanediamine to give the above modified ODNs. The thermal stability, **resistance** toward **nuclease** digestion, and stability in fetal calf serum of the modified ODNs were studied. An increase in the number of 5-(N-**aminohexyl**)carbamoyl-2'-deoxyuridines (H) in the ODNs was found to effectively stabilize duplex formation with both the corresponding

complementary DNA and RNA and protect against nucleolytic hydrolysis by snake venom phosphodiesterase. In particular, the half-life of ODN 19, which contained four H residues, was about 162 h in the presence of the nuclease. Furthermore, 19 was also stable in medium containing 10% fetal calf serum with a t(1/2) of about 48 h, while t(1/2) for the corresponding unmodified ODN was 13 min.

L14 ANSWER 43 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:297595 BIOSIS
DOCUMENT NUMBER: PREV199799596798
TITLE: Inhibition of human cytomegalovirus DNA replication with a phosphorothioate cholesteryl-**modified oligonucleotide** is mediated by rapid cellular association and virus-facilitated nuclear localization.
AUTHOR(S): Zhang, Z.; Smith, J. A.; Smyth, A. P.; Tang, J.-Y.; Eisenberg, W.; Pari, G. S. (1)
CORPORATE SOURCE: (1) Hybridon Inc., 620 Memorial Dr., Cambridge, MA 02139 USA
SOURCE: Antiviral Chemistry & Chemotherapy, (1997) Vol. 8, No. 3, pp. 255-264.
ISSN: 0956-3202.
DOCUMENT TYPE: Article
LANGUAGE: English
AB We have previously shown that an antisense phosphorothioate (PS) oligodeoxynucleotide has potent anti-human cytomegalovirus (HCMV) activity (GS Pari, AK Field & JA Smith, Antimicrobiol Agents and Chemotherapy 1995, 39: 1157-1161). We have now used a **modified** PS **oligonucleotide** having three **2'**-O-methyl nucleotides at the 3' end and four 2'-O-methyl nucleotides at the 5' end, containing a cholesterol moiety linked to the 3' end by a novel **thiono** -triester linkage. This compound, UL36ANTI-M, is superior to the PS (UL36ANTI) version with respect to antiviral potency, melting temperature and **nuclease resistance**. Also, we show that cellular association for this oligonucleotide is rapid, occurring within 15 min after treatment and is about 12-fold higher when compared to UL36ANTI. This increased rate of cellular association also correlates with antiviral properties in that a 15 min incubation with UL36ANTI-M was sufficient to achieve 75% inhibition of viral DNA replication and complete inhibition was achieved after only a 1 h pretreatment. In addition confocal microscopic examination showed a change in subcellular distribution from perinuclear to nuclear for oligonucleotides in HCMV-infected human fibroblasts. However, the total amount of cell-associated oligonucleotide was unchanged in infected cells.

L14 ANSWER 44 OF 67 MEDLINE
ACCESSION NUMBER: 97187656 MEDLINE
DOCUMENT NUMBER: 97187656 PubMed ID: 9035109
TITLE: Potent 2'-amino-, and 2'-fluoro-2'-deoxyribonucleotide RNA inhibitors of keratinocyte growth factor.
AUTHOR: Pagratis N C; Bell C; Chang Y F; Jennings S; Fitzwater T; Jellinek D; Dang C
CORPORATE SOURCE: NeXstar Pharmaceuticals, Inc., Boulder, CO 80301, USA.
SOURCE: NATURE BIOTECHNOLOGY, (1997 Jan) 15 (1) 68-73.
Journal code: 9604648. ISSN: 1087-0156.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970414
Last Updated on STN: 19970414
Entered Medline: 19970401

AB Reiterative in vitro selection-amplification from random **oligonucleotide** libraries allows the identification of molecules with specific functions such as binding to specific proteins. The therapeutic usefulness of such molecules depends on their high affinity and **nuclease resistance**. Libraries of RNA molecules containing 2'amino-(2'NH2)- or 2'fluoro-(2'F)-2'-deoxypyrimidines could yield ligands with similar **nuclease resistance** but not necessarily with similar affinities. This is because the intramolecular helices containing 2'NH2 have lower melting temperatures (Tm) compared with helices containing 2'F, giving them thermodynamically less stable structures and possibly weaker affinities. We tested these ideas by isolating high-affinity ligands to human keratinocyte growth factor from libraries containing **modified** RNA molecules with either 2'NH2 or 2'F pyrimidines. We demonstrated that 2'F RNA ligands have affinities (Kd approximately 0.3-3 pM) and bioactivities (Ki approximately 34 pM) superior to 2'NH2 ligands (Kd approximately 400 pM and Ki approximately 10 nM). In addition, 2'F ligands have extreme thermo-stabilities (Tm approximately 78 degrees C in low salt, and specificities).

L14 ANSWER 45 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 126:99308 CA
TITLE: **Antisense oligonucleotide** modulation of raf gene expression
INVENTOR(S): Monia, Brett P.; Martin, Pierre; Altmann, Karl-Heinz
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA; CIBA-Geigy Ltd.; Monia, Brett P.; Martin, Pierre; Altmann, Karl-Heinz
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9639415	A1	19961212	WO 1996-US8165	19960531
W: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5744362	A	19980428	US 1995-463912	19950605
AU 9659593	A1	19961224	AU 1996-59593	19960531
EP 863911	A1	19980916	EP 1996-916859	19960531
EP 863911	B1	20020424		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
BR 9608402	A	19991026	BR 1996-8402	19960531
JP 3054745	B2	20000619	JP 1997-500901	19960531
JP 10508760	T2	19980902		
AT 216705	E	20020515	AT 1996-916859	19960531

PRIORITY APPLN. INFO.:
US 1995-463912 A 19950605
US 1994-250856 A2 19940531
WO 1996-US8165 W 19960531

AB **Oligonucleotides** are provided which are targeted to **nucleic acids** encoding human c-raf and capable of inhibiting raf expression. **Oligonucleotides** targeted to the 3'-UTR of the raf gene (5'-tcccgcctgtgacatgcatt-3') showed >90% inhibition of c-raf mRNA expression in T24 bladder carcinoma cells and decreased tumor size at all doses (0.006-6.0 mg/kg) in nude mice in a dose-dependent

manner. The **oligonucleotides** contain a methoxyethoxy (2'-O-CH2CH2OCH3) **modification** at the 2' position of at least one nucleotide; this **modification** increases both the affinity of the **oligonucleotide** for its target and **nuclease resistance** of the **oligonucleotide**. Inhibitory effects were also obsd. with MDA-MB 231 human breast carcinoma tumors, human colon carcinoma tumors, and A549 human lung adenocarcinoma. The present invention comprises methods of inhibiting hyperproliferation of cells and methods of treating abnormal proliferative conditions which employ the described **oligonucleotides**.

L14 ANSWER 46 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 124:283703 CA
TITLE: Conjugates of metal complexes and **oligoribonucleotides** which bind specifically to selected target structures for MRI
INVENTOR(S): Platzek, Johannes; Niedballa, Ulrich; Raduechel, Bernd; Muehler, Andreas; Speck, Ulrich
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger. Offen., 19 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4424923	A1	19960118	DE 1994-4424923	19940714
WO 9602669	A1	19960201	WO 1995-EP2686	19950712
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9531090	A1	19960216	AU 1995-31090	19950712
EP 770146	A1	19970502	EP 1995-926850	19950712
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10511842	T2	19981117	JP 1995-504000	19950712
ZA 9505894	A	19960730	ZA 1995-5894	19950714
PRIORITY APPLN. INFO.:			DE 1994-4424923	19940714
			DE 1994-4445076	19941205
			WO 1995-EP2686	19950712

AB Conjugates of **modified oligonucleotides** with metal complexes or complexing agents, which bind specifically to biol. target structures, are useful in diagnostic NMR imaging. The **oligonucleotides** are **modified** to render them **resistant** to **degrdn**. by endogenous nucleases, e.g. by O-**alkylation**, **halogenation**, amination, or redn. at the 2' position or by replacement of phosphodiester groups by phosphorothioate, phosphorodithioate, or **alkylphosphonate** linkages. The **oligonucleotides** are selected from a random mixt. for binding to a target such as a non-**nucleic acid** macromol., tissue, or organ. Thus, a 30-mer **oligonucleotide** ligand for serine proteinase was conjugated with the linker .beta.-cyanoethyl S-trityl-6-mercaptohexyl N,N-diisopropylphosphoramidite, then with 1,4,7,10-tetraaza-2-[(5-aza-8-maleimido-6-oxo)octyl]cyclododecane-1,4,7,10-tetraacetic acid, and complexed with Gd3+ for use in NMR imaging.

L14 ANSWER 47 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 124:254781 CA
TITLE: Conjugates of metal complexes and **oligoribonucleotides** which bind specifically

to selected target structures

INVENTOR(S): Dinkelborg, Ludger; Hilger, Christoph-Stephan; Niedballa, Ulrich; Platzek, Johannes; Raduechel, Bernd; Speck, Ulrich

PATENT ASSIGNEE(S): Schering A.-G., Germany

SOURCE: Ger. Offen., 25 pp.
CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4424922	A1	19960118	DE 1994-4424922	19940714
US 2002077306	A1	20020620	US 1995-488290	19950607
IL 114237	A1	20000831	IL 1995-114237	19950620
CA 2194558	AA	19960201	CA 1995-2194558	19950630
WO 9602274	A1	19960201	WO 1995-EP2539	19950630
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9529791	A1	19960216	AU 1995-29791	19950630
EP 777498	A1	19970611	EP 1995-925792	19950630
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1152879	A	19970625	CN 1995-194000	19950630
HU 76329	A2	19970828	HU 1997-100	19950630
JP 10503182	T2	19980324	JP 1995-504630	19950630
RU 2165771	C2	20010427	RU 1997-102039	19950630
ZA 9505895	A	19960219	ZA 1995-5895	19950714
NO 9700141	A	19970314	NO 1997-141	19970113
AU 9920360	A1	19990617	AU 1999-20360	19990312
AU 721330	B2	20000629		

PRIORITY APPLN. INFO.:

DE 1994-4424922	A	19940714
US 1994-336127	B2	19941104
US 1994-336128	B2	19941104
DE 1994-4445078	A	19941205
US 1994-357573	B2	19941215
US 1994-358065	B2	19941215
US 1995-409813	B1	19950324
AU 1995-29791	A3	19950630
WO 1995-EP2539	W	19950630

AB Conjugates of **modified oligonucleotides** with complexes of radioactive or stable metal isotopes, which bind specifically to biol. target structures, are useful in diagnostic imaging and radiotherapy. The **oligonucleotides** are **modified** to render them **resistant** to **degrdn.** by endogenous nucleases, e.g. by O-**alkylation, halogenation**, amination, or redn. at the 2' position or by replacement of phosphodiester groups by phosphorothioate, phosphorodithioate, or **alkylphosphonate** linkages. The **oligonucleotides** are selected from a random mixt. for binding to a target such as a non-**nucleic acid** macromol., tissue, or organ. Thus, a 30-mer **oligonucleotide** ligand for NGF was conjugated with the linker .beta.-cyanoethyl N,N-diisopropylamino-6-(trifluoroacetamido)-1-hexylphosphoramidite, then with 10-[7-(4-isothiocyanatophenyl)-2-hydroxy-5-oxo-7-(carboxymethyl)-4-azaheptyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (prepn. given), and complexed with 111In(III) for use as a radiodiagnostic agent.

L14 ANSWER 48 OF 67 CA

ACCESSION NUMBER: 125:158040 CA
TITLE: In vitro efficacy of morpholino-**modified** **antisense oligomers** directed against tumor necrosis factor-.alpha. mRNA
AUTHOR(S): Taylor, Margaret Flynn; Paulauskis, Joseph D.; Weller, Dwight D.; Kobzik, Lester
CORPORATE SOURCE: Physiol. Program, Harvard Sch. Public Health, Boston, MA, 02115, USA
SOURCE: Journal of Biological Chemistry (1996), 271(29), 17445-17452
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Chem. **modification** of **antisense** **oligonucleotides** to increase **nuclease resistance** may improve their efficacy within enzyme-rich cellular targets (e.g. macrophages). We evaluated a panel of morpholino **antisense** **oligomers** (M-AS) for their ability to inhibit macrophage tumor necrosis factor-.alpha. (TNF-.alpha.) release and compared them to phosphodiester (O-AS) and phosphorothioate (S-AS) types of **oligonucleotides**. M-AS inhibited translation in vitro (rabbit reticulocyte lysate) of target mRNA at concns. as low as 200 nM (e.g. percent inhibition by M-AS 2 at 0.2, 1.0, and 2.0 .mu.M was 40.9 .+-. 5.3%, 50.2 .+-. 4.6%, and 57.7 .+-. 3.6%, resp., n = 4, p .ltoreq. 0.002 vs. control). Similarly, M-AS 2 effectively, albeit partially, inhibited TNF-.alpha. prodn. by LPS-stimulated macrophages (RAW 264.7 cells). Incubation of cells with 25 .mu.M M-AS 2 resulted in 32.6 .+-. 2.6% (n = 3, p = 0.002 vs. control) decrease in TNF-.alpha. release. In contrast, S-AS inhibited translation of the target mRNA in the rabbit reticulocyte lysate assay, but not in the cell-based assay. In fact, S-AS nonspecifically augmented TNF-.alpha. release. O-AS were without effect in either system. Uptake studies with fluorescent M-AS revealed that inhibitory effects were seen despite relatively low cellular uptake (intracellular concn. 30.5 .+-. 6.7 nM; efficiency of uptake 0.1%). In contrast, flow cytometric and confocal anal. revealed that S-AS were avidly taken up by RAW 264.7 cells, confirming that their lack of efficacy was not due to lack of uptake. With improved methods of delivery, M-AS may represent an important therapeutic modality.

L14 ANSWER 49 OF 67 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 96278923 MEDLINE
DOCUMENT NUMBER: 96278923 PubMed ID: 8662854
TITLE: **Nuclease resistance** and **antisense** activity of **modified** **oligonucleotides** targeted to Ha-ras.
AUTHOR: Monia B P; Johnston J F; Sasmor H; Cummins L L
CORPORATE SOURCE: Department of Molecular Pharmacology and Division of Medicinal Chemistry, Isis Pharmaceuticals, Carlsbad, California 92008, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Jun 14) 271 (24) 14533-40.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-J00277
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960828
Last Updated on STN: 19970203

Entered Medline: 19960820

AB We have previously described structure-activity studies on a 17-mer uniform phosphorothioate antisense sequence targeted to human Ha-ras. In an effort to further improve the pharmacological properties of antisense oligonucleotides, structure-activity studies on this 17-mer sequence were expanded to examine both the effects of replacing phosphorothioate backbone linkages with phosphodiester linkages and the effects of incorporating various **2'-sugar modifications** into phosphorothioate and phosphodiester oligonucleotides on oligonucleotide stability against nucleases in vitro and on antisense activity in cells. Replacement of three or more phosphorothioate linkages with phosphodiester linkages greatly compromised both **nuclease resistance** and antisense activity, and these effects correlated directly with the number of phosphodiester linkages incorporated into the oligonucleotide. However, substantial **nuclease resistance**, sufficient for obtaining potent antisense effects in cells, was conferred to phosphodiester oligonucleotides by incorporation of appropriate **2'-alkoxy** sugar **modifications**. Nuclease stability and **antisense** activity imparted by these sugar modifications in phosphodiester backbones correlated with the size of the 2'-**alkoxy** substituent (pentoxy > propoxy > methoxy > deoxy). Furthermore, antisense activity mediated by oligonucleotides that exhibit partial **resistance** to **nucleolytic degradation** was dependent on both oligonucleotide concentration and the duration of oligonucleotide treatment.

L14 ANSWER 50 OF 67 MEDLINE

ACCESSION NUMBER:	97133444 MEDLINE
DOCUMENT NUMBER:	97133444 PubMed ID: 8978841
TITLE:	**2'-O-aminopropyl** ribonucleotides: a zwitterionic **modification** that enhances the exonuclease resistance and biological activity of **antisense oligonucleotides**.
AUTHOR:	Griffey R H; Monia B P; Cummins L L; Freier S; Greig M J; Guinosso C J; Lesnik E; Manalili S M; Mohan V; Owens S; Ross B R; Sasmor H; Wancewicz E; Weiler K; Wheeler P D; Cook P D
CORPORATE SOURCE:	Isis Pharmaceuticals, Carlsbad, California 92008, USA.
SOURCE:	JOURNAL OF MEDICINAL CHEMISTRY, (1996 Dec 20) 39 (26) 5100-9. Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	199701
ENTRY DATE:	Entered STN: 19970219 Last Updated on STN: 19980206 Entered Medline: 19970124

AB **Oligonucleotides** containing 2'-O-**aminopropyl**-substituted RNA have been synthesized. The 2'-O-(**aminopropyl**)adenosine (APA), 2'-O-(**aminopropyl**)cytidine (APC), 2'-O-(**aminopropyl**)-guanosine (APG), and 2'-O-(**aminopropyl**)uridine (APU) have been prepared in high yield from the ribonucleoside, protected, and incorporated into an **oligonucleotide** using conventional phosphoramidite chemistry. Molecular dynamics studies of a dinucleotide in water demonstrates that a short **alkylamine** located off the 2'-oxygen of ribonucleotides alters the sugar pucker of the nucleoside but does not form a tight ion pair with the proximate phosphate. A 5-mer with the sequence ACTUC has been characterized using NMR. As predicted from the modeling results, the sugar pucker of the APU moiety is shifted toward a C3'-endo geometry. In addition, the primary

amine rotates freely and is not bound electrostatically to any phosphate group, as evidenced by the different sign of the NOE between sugar proton resonances and the signals from the propylamine chain. Incorporation of **aminopropyl** nucleoside residues into point-substituted and fully **modified oligomers** does not decrease the affinity for complementary RNA compared to 2'-O-**alkyl** substituents of the same length. However, two APU residues placed at the 3'-terminus of an **oligomer** gives a 100-fold increase in **resistance** to exonuclease **degradation**, which is greater than observed for phosphorothioate **oligomers**. These structural and biophysical characteristics make the 2'-O-**aminopropyl** group a leading choice for incorporation into **antisense** therapeutics. A 20-mer phosphorothioate **oligonucleotide** capped with two phosphodiester **aminopropyl** nucleotides targeted against C-raf mRNA has been transfected into cells via electroporation. This **oligonucleotide** has 5-10-fold greater activity than the control phosphorothioate for reducing the abundance of C-raf mRNA and protein.

L14 ANSWER 51 OF 67 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 96173637 MEDLINE
DOCUMENT NUMBER: 96173637 PubMed ID: 8602351
TITLE: Enhanced activity of an antisense oligonucleotide targeting murine protein kinase C-alpha by the incorporation of **2**'-O-propyl **modifications**.
AUTHOR: McKay R A; Cummins L L; Graham M J; Lesnik E A; Owens S R; Winniman M; Dean N M
CORPORATE SOURCE: Department of Molecular Pharmacology, Isis Pharmaceuticals, Carlsbad, CA 92008, USA.
SOURCE: NUCLEIC ACIDS RESEARCH, (1996 Feb 1) 24 (3) 411-7. Journal code: 0411011. ISSN: 0305-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199605
ENTRY DATE: Entered STN: 19960517
Last Updated on STN: 19960517
Entered Medline: 19960507

AB We have previously described the characterization of a 20mer phosphorothioate oligodeoxynucleotide (ISIS 4189) which inhibits murine protein kinase C-alpha (PKC-alpha) gene expression, both in vitro and in vivo. In an effort to increase the antisense activity of this **oligonucleotide**, **2**'-O-propyl **modifications** have been incorporated into the 5'- and 3'-ends of the oligonucleotide, with the eight central bases left as phosphorothioate oligodeoxynucleotides. Hybridization analysis demonstrated that these modifications increased affinity by approximately 8 and 6 degrees C per oligonucleotide for the phosphodiester (ISIS 7815) and phosphorothioate (ISIS 7817) respectively when hybridized to an RNA complement. In addition, 2'-O-propyl incorporation greatly enhanced the **nuclease resistance** of the oligonucleotides to snake venom phosphodiesterase or intracellular nucleases in vivo. The increase in affinity and nuclease stability of ISIS 7817 resulted in a 5-fold increase in the ability of the oligonucleotide to inhibit PKC-alpha gene expression in murine C127 cells, as compared with the parent phosphorothioate oligodeoxynucleotide. Thus an RNase H-dependent phosphorothioate **oligodeoxynucleotide** can be **modified** as a **2** '-O-propyl 'chimeric' oligonucleotide to provide a significant increase in antisense activity in cell culture.

L14 ANSWER 52 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 124:146761 CA

TITLE: Backbone-**modified oligonucleotide** analogs and solid phase synthesis
INVENTOR(S): Cock, Phillip Dan; Sanghvi, Yogesh S.; Morvan, Francois
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 100
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9518136	A1	19950706	WO 1994-US14883	19941228
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5541307	A	19960730	US 1993-174379	19931228
EP 737201	A1	19961016	EP 1995-906115	19941228
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AU 713740	B2	19991209	AU 1997-26244	19970624
AU 9726244	A1	19971106		
US 6232463	B1	20010515	US 1998-128508	19980804

PRIORITY APPLN. INFO.:

US 1993-174379	A	19931228
US 1990-558663	A2	19900727
US 1990-566836	A2	19900813
US 1991-703619	A2	19910521
US 1992-903160	B2	19920624
AU 1993-38025	A3	19930225
US 1993-40903	A2	19930331
WO 1994-US14883	W	19941228
US 1997-948151	A1	19971009

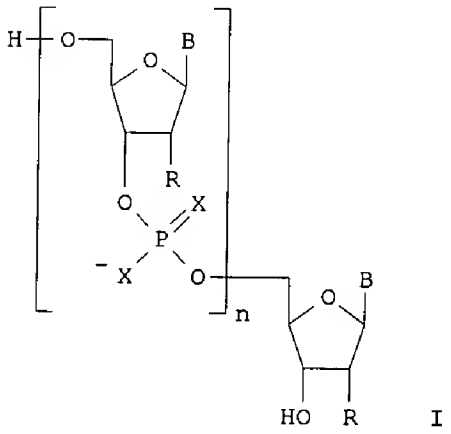
AB Compds. and methods for prepg. **nuclease-resistant oligonucleotide** analogs are provided. In preferred embodiments, the methods involve solid-phase coupling of synthons bearing either 3'-electrophilic groups and 5'-nucleophilic groups or 5'-electrophilic groups and 3'-nucleophilic groups to form neutral, achiral **oligomers**. In particular, amine-terminated synthons are coupled with aldehyde-terminated synthons to produce hydroxylamino- and/or hydrazino-contg. covalent linkages. Examples illustrate prepn. of a variety of nucleotide analogs, various nucleotide dimer and tetramer analogs contg. the novel linkages, and **oligonucleotide** analogs contg. both the novel and std. linkages. For instance, coupling of 5'-O-**amino**-N4-benzoyl-3'-O-tert-butyldiphenylsilyl-5-methyl-2'-deoxycytidine with 5'-O-tert-butyldiphenylsilyl-3'-deoxy-3'-C-formylthymidine to give an oxime, followed by deprotection of the benzamide function with NH3/MeOH, redn. of the oxime function with NaBH3CN, and reductive N-methylation with formaldehyde and NaBH3CN, gave the dimer TBDPS-O-T*MeC-O-TBDPS [TBDPS = tert-butyldiphenylsilyl; * = 3'-CH2NMeO-5' (hereafter "MMI") linkage; Me = 5-methyl] in 84% yield. This dimer was subjected to N-benzoylation, desilylation, tritylation, and phosphitylation, to give the dimer DMT-O-T*MeCBz-O-Amidite [DMT = 4,4'-dimethoxytrityl; Amidite = P(NPr-iso2)OCH2CH2CN; Bz = N4-benzoyl]. This and similar MMI-linkage dimers and tetramers were used to prep. chimeric **oligonucleotides** such as T*TPSC*TPSCPSGPSCPSTPSGPSGPSTP SGPSAPSGPST*TPST*C (code no. 9495; I; PS = phosphorothioate linkage). As an **antisense oligonucleotide** for PKC-.alpha. mRNA in A549 cells, I showed greater activity (IC50 = 80 nM) than the analogous std. **oligonucleotide** sequence with pure phosphorothioate linkages (IC50 = 175 nM).

L14 ANSWER 53 OF 67 CA COPYRIGHT 2003 ACS

ACCESSION NUMBER: 124:30273 CA
TITLE: Preparation of **modified oligonucleotides** as active substances.
INVENTOR(S): Noe, Christian; Brunar, Helmut
PATENT ASSIGNEE(S): Austria
SOURCE: PCT Int. Appl., 5 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9516696	A2	19950622	WO 1994-AT195	19941213
WO 9516696	A3	19950720		
W: AU, CA, CN, CZ, HU, JP, KR, NO, PL, RO, RU, SI, SK, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AT 9302505	A	20000915	AT 1993-2505	19931213
AT 407639	B	20010525		
AU 9511025	A1	19950703	AU 1995-11025	19941213

PRIORITY APPLN. INFO.: AT 1993-2505 A 19931213
WO 1994-AT195 W 19941213
OTHER SOURCE(S): MARPAT 124:30273
GI



I

AB Title compds. (I; n = 10-50; B = nucleotide base; X = O, S; R = H, OANHR1; A = **alkylene**; R1 = **alkyl**), were prepd. These **modified oligonucleotides** do not lose their ability to pair with their complementary strand. They can be expected to show greater **nuclease resistance** and better membrane penetrability than natural oligonucleotides, which yields important benefits for antisense therapy. Thus, adenosine in DMF was treated with NaH and then N-(6-**iodohexyl**)trifluoroacetamide at 0-40.degree. to give 2'-O-(6-Trifluoroacetylaminohexyl)adenosine. This was used to prep. several **modified** adenosine **oligonucleotides**, including A*A*A*A*A*A*AAAAAA (A* = **2'-aminohexyl-modified** adenosine residue). Use of I as virucides and anticancer drugs is claimed.

L14 ANSWER 54 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 123:228796 CA
TITLE: Backbone **modified oligonucleotide** analogs and their preparation through reductive coupling
INVENTOR(S): Sanghvi, Yogesh S.; Cook, Phillip D.
PATENT ASSIGNEE(S): Isis Pharmaceuticals, USA
SOURCE: U.S., 31 pp. Cont.-in-part of U.S. Ser. No. 903,160.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 100
PATENT INFORMATION:

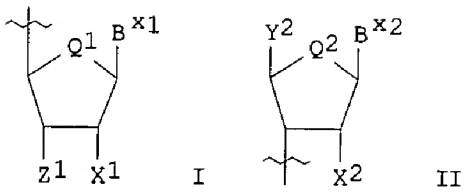
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5386023	A	19950131	US 1993-40903	19930331
US 5138045	A	19920811	US 1990-558663	19900727
US 5223618	A	19930629	US 1990-566836	19900813
US 5378825	A	19950103	US 1991-703619	19910521
US 5541307	A	19960730	US 1993-174379	19931228
US 5783682	A	19980721	US 1994-180124	19940111
WO 9422883	A1	19941013	WO 1994-US3212	19940324
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5808023	A	19980915	US 1994-335046	19941107
US 5834607	A	19981110	US 1994-361858	19941222
US 6121433	A	20000919	US 1996-669300	19960808
US 5965722	A	19991012	US 1997-848840	19970430
AU 713740	B2	19991209	AU 1997-26244	19970624
AU 9726244	A1	19971106		
US 6271357	B1	20010807	US 1998-118654	19980717
US 6232463	B1	20010515	US 1998-128508	19980804
US 6025482	A	20000215	US 1998-152958	19980914

PRIORITY APPLN. INFO.:

US 1990-558663	A2	19900727
US 1990-566836	A2	19900813
US 1991-703619	A2	19910521
US 1992-903160	A2	19920624
US 1991-801168	B1	19911120
US 1991-814961	B2	19911224
US 1992-844845	A2	19920303
WO 1992-US4294	A2	19920521
US 1992-943516	B1	19920911
US 1992-958134	B2	19921005
WO 1992-US11339	B1	19921223
US 1993-7996	B2	19930121
AU 1993-38025	A3	19930225
US 1993-39846	B2	19930330
US 1993-39979	B2	19930330
US 1993-40526	A2	19930331
US 1993-40903	A2	19930331
US 1993-40933	B2	19930331
WO 1993-US9346	B1	19931001
US 1994-180124	A2	19940111
US 1994-227180	A2	19940413
US 1994-244993	A2	19940621
US 1994-300072	A3	19940902
US 1994-317289	A2	19941003
US 1994-335046	A2	19941107
WO 1995-US350	W	19950111
US 1995-411734	A2	19950403
US 1995-465866	A2	19950606

US 1995-468037 A2 19950606
US 1995-488256 A2 19950607
US 1997-794493 A2 19970204
US 1997-948151 A1 19971009

OTHER SOURCE(S): MARPAT 123:228796
GI



AB Methods for prepg. oligonucleotide analogs which have improved **nuclease resistance** and improved cellular uptake (no data) are provided. A method for forming between adjacent sugar moieties a covalent linkage having structure CH:NRACH2, CH2RAN:CH, or RAN:CHCH2 where RA is O or NR1, comprising the steps of: (a) providing synthons having structures I and II; (b) contacting said synthons for a time and under reaction conditions effective to form said covalent linkage; wherein: Z1 and Y2 are selected such that (i) Z1 is C(O)H and Y2 is CH2RANH2 ; or (ii) Z1 is CH2RANH2 and Y2 is C(O)H; or (iii) Z1 is RANH2 and Y2 is H(O)CCH2 ; R1 is H or **alkyl** having 1 to about 10 carbon atoms; BX1 and BX2 are, independently, nucleosidic bases; Q1 and Q2 are O; and X1 and X2 are, independently, H; OH; F; or O-**alkyl** having 1 to about 10 carbon atoms. The oligonucleotide analogs have improved **nuclease resistance** and improved cellular uptake (no data). Authors caution safety in prepn. of 3'-C-cyano-3'-deoxy-5'-O-tritylthymidine.

L14 ANSWER 55 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 122:151411 CA
TITLE: Preparation of backbone-**modified oligonucleotide** analogs for therapeutic use
INVENTOR(S): Cook, Philip D.; Sanghvi, Yogesh S.
PATENT ASSIGNEE(S): ISIS Pharmaceuticals, Inc., USA
SOURCE: U.S., 19 pp. Cont.-in-part of U.S. 5,223,618.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 100
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5378825	A	19950103	US 1991-703619	19910521
US 5138045	A	19920811	US 1990-558663	19900727
US 5223618	A	19930629	US 1990-566836	19900813
CA 2103378	AA	19921122	CA 1992-2103378	19920521
CA 2103464	AA	19921122	CA 1992-2103464	19920521
WO 9220822	A1	19921126	WO 1992-US4294	19920521
W: AU, BR, CA, FI, HU, JP, KR, NO, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
WO 9220823	A1	19921126	WO 1992-US4305	19920521
W: AU, BR, CA, FI, HU, JP, KR, NO, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				

AU 9219986	A1	19921230	AU 1992-19986	19920521
AU 662538	B2	19950907		
AU 9221502	A1	19921230	AU 1992-21502	19920521
AU 666121	B2	19960201		
EP 586520	A1	19940316	EP 1992-912190	19920521
EP 586520	B1	20000419		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				
EP 586570	A1	19940316	EP 1992-913119	19920521
EP 586570	B1	20000913		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				
JP 06504067	T2	19940512	JP 1992-500301	19920521
HU 65941	A2	19940829	HU 1993-3290	19920521
HU 66378	A2	19941128	HU 1993-3289	19920521
BR 9206026	A	19941227	BR 1992-6026	19920521
BR 9206027	A	19941227	BR 1992-6027	19920521
AT 191933	E	20000515	AT 1992-912190	19920521
EP 1004593	A2	20000531	EP 1999-203016	19920521
EP 1004593	A3	20000719		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC				
AT 196321	E	20000915	AT 1992-913119	19920521
US 5386023	A	19950131	US 1993-40903	19930331
US 5489677	A	19960206	US 1993-40526	19930331
NO 9304180	A	19940111	NO 1993-4180	19931118
NO 9304179	A	19940112	NO 1993-4179	19931118
US 5541307	A	19960730	US 1993-174379	19931228
US 5783682	A	19980721	US 1994-180124	19940111
US 5610289	A	19970311	US 1994-150079	19940407
US 5602240	A	19970211	US 1994-140206	19940425
US 5618704	A	19970408	US 1994-300072	19940902
US 5608046	A	19970304	US 1994-314877	19940929
US 5792844	A	19980811	US 1994-317289	19941003
US 5808023	A	19980915	US 1994-335046	19941107
US 5834607	A	19981110	US 1994-361858	19941222
US 5677437	A	19971014	US 1995-392675	19950223
US 5623070	A	19970422	US 1995-395168	19950227
US 6087482	A	20000711	US 1995-522374	19950918
US 6121433	A	20000919	US 1996-669300	19960808
US 5688941	A	19971118	US 1996-760848	19961205
US 5965721	A	19991012	US 1996-763354	19961211
US 5777092	A	19980707	US 1997-795282	19970204
US 5969118	A	19991019	US 1997-794493	19970204
US 5998603	A	19991207	US 1997-809239	19970520
AU 713740	B2	19991209	AU 1997-26244	19970624
AU 9726244	A1	19971106		
US 6271357	B1	20010807	US 1998-118654	19980717
US 6214551	B1	20010410	US 1998-123572	19980727
US 6232463	B1	20010515	US 1998-128508	19980804
US 6025482	A	20000215	US 1998-152958	19980914
US 6320040	B1	20011120	US 1999-414146	19991007
US 2003045705	A1	20030306	US 2002-153320	20020522
US 2002183502	A1	20021205	US 2002-155950	20020524

PRIORITY APPLN. INFO.:

US 1990-558663	A2	19900727
US 1990-566836	A2	19900813
US 1991-703619	A	19910521
WO 1991-US5713	B2	19910812
US 1992-844845	A2	19920303
EP 1992-913119	A3	19920521
WO 1992-US4294	A	19920521
WO 1992-US4305	A	19920521
US 1992-903160	A2	19920624
US 1992-943516	B1	19920911
AU 1993-38025	A3	19930225

US 1993-39846	B2	19930330
US 1993-39979	B2	19930330
US 1993-40526	A2	19930331
US 1993-40903	A2	19930331
US 1993-40933	B2	19930331
US 1994-180124	A2	19940111
WO 1994-US3536	W	19940330
US 1994-150079	A3	19940407
US 1994-140206	A3	19940425
US 1994-300072	A3	19940902
US 1994-314877	A2	19940929
US 1994-317289	A3	19941003
US 1994-335046	A3	19941107
WO 1995-US350	W	19950111
US 1995-395168	A3	19950227
WO 1995-US13038	W	19950929
US 1996-763354	A2	19961211
US 1996-768780	B1	19961213
US 1997-809239	A1	19970520
US 1997-948151	A1	19971009
US 1998-58470	B1	19980410

OTHER SOURCE(S): MARPAT 122:151411

AB Therapeutic oligonucleotide analogs which have improved **nuclease resistance** and improved cellular uptake are provided. Replacement of the normal phosphorodiester inter-sugar linkages found in wild type oligomers with four atom linking groups forms unique di- and poly-nucleosides and nucleotides useful in regulating RNA expression and in therapeutics. Methods of synthesis and use are also disclosed. Prepn. of e.g. an oxime-linked dinucleoside from 3'-deoxy-3'-C-formyl-5'-O-tritylthymidine and 5'-O-**amino**-3'-O-tert-butyl(diphenyl)silylthymidine is described. Also described are evaluation procedures by hybridization anal., **nuclease resistance**, and lipoxygenase anal.

L14 ANSWER 56 OF 67 MEDLINE

ACCESSION NUMBER: 96009621 MEDLINE
DOCUMENT NUMBER: 96009621 PubMed ID: 7547864
TITLE: Potent 2'-amino-2'-deoxypyrimidine RNA inhibitors of basic fibroblast growth factor.
AUTHOR: Jellinek D; Green L S; Bell C; Lynott C K; Gill N; Vargeese C; Kirschenheuter G; McGee D P; Abesinghe P; Pieken W A; +
CORPORATE SOURCE: NeXstar Pharmaceuticals, Inc., Boulder, Colorado 80301, USA.
SOURCE: BIOCHEMISTRY, (1995 Sep 12) 34 (36) 11363-72.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951227
Last Updated on STN: 19951227
Entered Medline: 19951025

AB Screening of random **oligonucleotide** libraries with SELEX [systematic evolution of ligands by exponential enrichment; Tuerk, C., & Gold, L. (1990) Science 249, 505-510] has emerged as a powerful method for identifying high-affinity **nucleic acid** ligands for a wide range of molecular targets. Nuclease sensitivity of unmodified RNA and DNA, however, imposes considerable restrictions on their use as therapeutics or diagnostics. **Modified** RNA in which pyrimidine **2'**-hydroxy groups have been substituted with 2'-amino groups (2'-aminopyrimidine RNA) is known to be substantially more

resistant to serum **nucleases**. We report here on the use of SELEX to identify high-affinity 2'-aminopyrimidine RNA ligands to a potent angiogenic factor, basic fibroblast growth factor (bFGF). High-affinity ligands with the same consensus primary structure have been isolated from two independent libraries of approximately 6 x 10(14) molecules containing 30 or 50 randomized positions. Compared to unmodified RNA with the same sequence, 2'-aminopyrimidine ligands are at least 1000-fold more stable in 90% human serum. The sequence information required for high-affinity binding to bFGF is contained within 24-26 nucleotides. The minimal ligand m21A (5'-GGUGUGUGGAAGACAGCGGGUGGUUC-3'; G = guanosine, A = adenosine, C = 2'-amino-2'-deoxycytidine, U = 2'-amino-2'-deoxyuridine, and C = 2'-amino-2'-deoxycytidine or deoxycytidine) binds to bFGF with an apparent dissociation constant (Kd) of 3.5 +/- 0.3) x 10(-10) M at 37 degrees C in phosphate-buffered saline (pH 7.4). Disassociation of m21A from bFGF is adequately described with a first-order rate constant of (1.96 +/- 0.08) x 10(-3) s-1 (t1/2 = 5.9 min). The calculated value for the association rate constant (kon = k(off)/Kd) was 5.6 x 10(6) M-1 s-1. Highly specific binding of m21A to bFGF was observed: binding to denatured bFGF, five proteins from the FGF family (acidic FGF, FGF-4, FGF-5, FGF-6, and FGF-7), and four other heparin binding proteins is substantially weaker under the same conditions with KdbFGF/Kdprotein values ranging from (4.1 +/- 1.4) x 10(-2) to > 10(-6). Heparin but not chondroitin sulfate competed for binding of m21A to bFGF. In cell culture, m21A inhibited [125I]bFGF binding to both low-affinity sites (ED50 approximately 1 nM) and high-affinity sites (ED50 approximately 3 nM) on CHO cells expressing transfected FGF receptor-1. (ABSTRACT TRUNCATED AT 400 WORDS)

L14 ANSWER 57 OF 67 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 95240995 EMBASE
DOCUMENT NUMBER: 1995240995
TITLE: Novel C5-substituted 2'-deoxyuridine derivatives bearing **amino**-linker arms: Synthesis, incorporation into oligodeoxyribonucleotides, and their hybridization properties.
AUTHOR: Ozaki H.; Nakamura A.; Arai M.; Endo M.; Sawai H.
CORPORATE SOURCE: Department of Chemistry, Faculty of Engineering, Gunma University, 1-5-1 Tenjin-cho,Kiryu, Gunma 376, Japan
SOURCE: Bulletin of the Chemical Society of Japan, (1995) 68/7. (1981-1987).
ISSN: 0009-2673 CODEN: BCSJA8
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB 2'-Deoxyuridine derivatives bearing several kinds of **amino**-linker arms at C5 position were synthesized from 5-(methoxycarbonylmethyl)-2'-deoxyuridine and ethylenediamine, 1,6-hexanediamine, or tris(2-**aminoethyl**)amine. The **modified** nucleosides were incorporated into oligodeoxyribonucleotides at one or three positions in place of thymidine residues. The thermal stability of the duplexes was investigated. Three incorporations of ethylenediamine or tris(2-**aminoethyl**)amine at the C5-position increase the duplex stability. The **amino**-linker arm affected the stability of the duplexes depending on the number of **amino** groups in the linker arm and the length of the arm. The linker arm improved the **nuclease resistance** at 5'-side phosphodiester linkage of the **modified** nucleoside in **oligodeoxyribonucleotides**.

L14 ANSWER 58 OF 67 SCISEARCH COPYRIGHT 2003 ISI (R)

ACCESSION NUMBER: 95:151912 SCISEARCH
THE GENUINE ARTICLE: QH281
TITLE: **ANTISENSE** 2'-O-ALKYL **OLIGORIBONUCLEOTIDES** ARE EFFICIENT INHIBITORS OF REVERSE TRANSCRIPTION
AUTHOR: BOIZIAU C; LARROUY B; SPROAT B S; TOULME J J (Reprint)
CORPORATE SOURCE: UNIV BORDEAUX 2, INSERM, U386, MOLEC BIOPHYS LAB, 146 RUE LEO SAIGNAT, F-33076 BORDEAUX, FRANCE (Reprint); UNIV BORDEAUX 2, INSERM, U386, MOLEC BIOPHYS LAB, F-33076 BORDEAUX, FRANCE; EUROPEAN MOLEC BIOL LAB, D-69012 HEIDELBERG, GERMANY
COUNTRY OF AUTHOR: FRANCE; GERMANY
SOURCE: NUCLEIC ACIDS RESEARCH, (11 JAN 1995) Vol. 23, No. 1, pp. 64-71.
ISSN: 0305-1048.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 20

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Reverse transcription is one step of the retroviral development which can be inhibited by **antisense oligonucleotides** **complementary** to the RNA template. 2'-O-Alkyl **oligoribonucleotides** are of interest due to their **nuclease resistance**, and to the high stability of the hybrids they form with RNA. **Oligonucleotides**, either fully or partly **modified** with 2'-O-alkyl residues, were targeted to an RNA template to prevent cDNA synthesis by the Avian Myeloblastosis Virus reverse transcriptase (AMV RT). Fully-**modified** 2'-O-allyl 17mers were able to specifically block reverse transcription via an RNase H-independent mechanism, with efficiencies comparable to those observed with phosphodiester (PO) and phosphorothioate **oligonucleotides**. Sandwich 2'-O-alkyl/PO/2'-O-alkyl **oligonucleotides**, supposed to combine the properties of 2'-O-alkyl **modifications** (physical blocking of the RT) to those of the PO window (RNase H-mediated cleavage of the RNA) were quasi-stoichiometric inhibitors when adjacent to the primer, but remained without any effect when non-adjacent. They were not able to compete with the polymerase and inhibited reverse transcription only through RNase H-mediated cleavage of the target.

L14 ANSWER 59 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 123:228785 CA
TITLE: Preparation of backbone **modified** **oligonucleotide** analogs through radical coupling
INVENTOR(S): Sanghvi, Yogesh S.; Cook, Phillip Dan
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 100
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9422894	A1	19941013	WO 1994-US3322	19940328
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 713740	B2	19991209	AU 1997-26244	19970624
AU 9726244	A1	19971106		

US 6232463 B1 20010515 US 1998-128508 19980804
PRIORITY APPLN. INFO.: US 1993-40933 A 19930331
AU 1993-38025 A3 19930225
US 1997-948151 A1 19971009
OTHER SOURCE(S): MARPAT 123:228785
AB Methods for prepg. **antisense oligonucleotide** analogs contg. azaalkylenes (CH2RANHCH2, (CH2)2NHRA, RANH(CH2)2, wherein RA = O, R1N and R1 = H, C1-10 **alkyl**, C2-10 alkenyl, C2-10 alkynyl, alkaryl, etc., all of which are optionally substituted) which have improved **nuclease resistance** and improved cellular uptake are provided. The **oligonucleotide** analogs can have altered sugar moieties, altered base moieties or altered inter-sugar linkages. In preferred embodiments, the methods involve radical coupling of 3'- and 5'-substituted or 5'- and 3'-substituted nucleosidic synthons. 3'-O-**amino**-5'-O-(tert-butyldimethylsilyl)thymidine (prepn. given), 3'-O-(tert-butyldimethylsilyl)thymidine-5'-aldehyde and AcOH ere stirred in CH2Cl2 to give the intermediate oxime, treated with NaCNBH3 to give the imine, which was treated with addnl. NaCNBH3 and aq. HCHO to give the methylated imine and this treated with B4N+ F- to give 3'-dephosphinico-3'-O-(methylimino)thymidylyl-(3'->5')-5'-deoxythymidine. Phosphodiesterase degrdn. was achieved with 5'-GCGTTTTT(3'-CH2NMeOCH2-4')TTTTTGCG3'. In a nuclease degrdn. study the tetramer TTTT which contains no phosphodiester linkage, showed complete stability >60 h of incubation in cell ext., suggesting that an end-capped (3' and 5') **oligomer** contg. achiral and neutral backbone will have enhanced half-life.

L14 ANSWER 60 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 122:182025 CA
TITLE: Immobilization of **nucleic acids** using capture probes with **modifications** that block enzymic **modification** and the use of electroluminescent reporter probes
INVENTOR(S): Kruse-Mueller, Cornelia; Berner, Sibylle; Kaletta, Cortina
PATENT ASSIGNEE(S): Boehringer Mannheim G.m.b.H., Germany
SOURCE: Eur. Pat. Appl., 38 p.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 628568	A2	19941214	EP 1994-108442	19940601
EP 628568	A3	19970305		
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE				
DE 4344742	A1	19941215	DE 1993-4344742	19931228
JP 07184696	A2	19950725	JP 1994-127416	19940609
US 5639609	A	19970617	US 1994-257778	19940609
US 6027885	A	20000222	US 1996-771256	19961220

PRIORITY APPLN. INFO.: DE 1993-4319151 19930609
DE 1993-4339086 19931116
DE 1993-4344742 19931228
US 1994-257778 19940609
OTHER SOURCE(S): MARPAT 122:182025
AB A method is described for immobilization of **nucleic acids** prepd. by enzymic **modification**, such as amplification, using capture probes that are **modified** to prevent their **modification** by the enzymes used, e.g. by blocking the ends or by use of base or sugar analogs. The use of these

modified oligonucleotides simplifies the anal. of amplification reactions because they can be incorporated into the amplification reaction. A similarly **modified** reporter probe carrying an electroluminescent reporter group is also described for use in quantification of the captured **nucleic acids**. The **modifications** may include **2'-O-alkylation** of the sugar, the use of a base analog such as deazapurine with the electroluminescent group linked to the base by a spacer group. The capture probe is preferably immobilized or it may carry a ligand that allows it to be bound to a derivatized surface. The method is demonstrated using biotinylated **oligonucleotides** as capture probes optionally using **oligonucleotides** contg. 2'-O-allyl nucleotides and a 3'-blocking group. The sensitivity of the method is comparable to the prior art; readings at high concns. (>1 pg) of **nucleic acids** are higher than in prior art methods with the lower endpoints comparable in the 10 fg range.

L14 ANSWER 61 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 120:2234 CA
TITLE: **Modified oligonucleotides** for recognition and cleavage of RNA and their use in disease treatment
INVENTOR(S): Cook, Phillip Dan; Bruice, Thomas; Guinosso, Charles John; Kawasaki, Andrew Mamoru; Griffey, Richard
PATENT ASSIGNEE(S): Isis Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 100
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9317717	A1	19930916	WO 1993-US2057	19930305
W: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG				
US 5359051	A	19941025	US 1992-846556	19920305
US 5514786	A	19960507	US 1992-942961	19920910
AU 9337944	A1	19931005	AU 1993-37944	19930305
JP 07502749	T2	19950323	JP 1993-515946	19930305
EP 656790	A1	19950614	EP 1993-907292	19930305
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 6358931	B1	20020319	US 1994-295744	19940830
AU 713740	B2	19991209	AU 1997-26244	19970624
AU 9726244	A1	19971106		
US 6232463	B1	20010515	US 1998-128508	19980804
US 2002160972	A1	20021031	US 2001-974326	20011010

PRIORITY APPLN. INFO.:

US 1992-846556	A	19920305
US 1992-942961	A2	19920910
US 1990-463358	B2	19900111
US 1990-566977	B2	19900813
WO 1991-US243	A2	19910111
AU 1993-38025	A3	19930225
WO 1993-US2057	A	19930305
US 1994-295744	A3	19940830
US 1997-948151	A1	19971009

AB The title **modified oligonucleotides** comprise an RNA cleaving moiety having at least general acid/base properties linked via an aryl or heteroaryl moiety to the **oligonucleotide**. The aryl or

heteroaryl moiety may be an intercalating group such as phenanthrene. The RNA cleaving moiety may be a (substituted) imidazole or bis-imidazole, or may be a structure which binds 1 or 2 metal ions. The **oligonucleotide** is preferably **modified** at the **2**' hydroxyl of the sugar. The synthesis of a representative **modified** nucleoside, 9-((4-(7-(-5-imidazoyl-1-H)naphthyl)-O-2-propyloxy-)b-D-ribofuranosyl))adenine, was presented. This nucleoside may be incorporated into an **antisense oligonucleotide** to prep. a **modified oligonucleotide** of the invention. Methods for screening of candidate **modified oligonucleotides** for specificity, **nuclease resistance**, and RNA cleavage activity are described.

L14 ANSWER 62 OF 67 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 93217953 MEDLINE
DOCUMENT NUMBER: 93217953 PubMed ID: 8464037
TITLE: Uniformly **modified 2**'-deoxy-**2**'-**fluoro** phosphorothioate oligonucleotides as **nuclease-resistant** antisense compounds with high affinity and specificity for RNA targets.
AUTHOR: Kawasaki A M; Casper M D; Freier S M; Lesnik E A; Zounes M C; Cummins L L; Gonzalez C; Cook P D
CORPORATE SOURCE: ISIS Pharmaceuticals, Carlsbad, California 92008.
SOURCE: JOURNAL OF MEDICINAL CHEMISTRY, (1993 Apr 2) 36 (7) 831-41. Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930521
Last Updated on STN: 19930521
Entered Medline: 19930430

AB "Uniformly" **modified** phosphodiester or phosphorothioate **oligonucleotides** incorporating **2**'-deoxy-2'-**fluoroadenosine**, -guanosine, -uridine, and -cytidine, reported herein for the first time, when hybridized with RNA afforded consistent additive enhancement of duplex stability without compromising base-pair specificity. CD spectra of the **2**'-deoxy-**2**'-**fluoro-modified oligonucleotides** hybridized with RNA indicated that the duplex adopts a fully A-form conformation. The **2**'-deoxy-**2**'-**fluoro-modified oligonucleotides** in phosphodiester form were not **resistant** to **nucleases**; however, the **modified** phosphorothioate **oligonucleotides** were highly **nuclease resistant** and retained exceptional binding affinity to the RNA targets. The stabilizing effects of the **2**'-deoxy-**2**'-**fluoro modifications** on RNA-DNA duplexes were shown to be superior to those of the 2'-O-methylribo substitutions. RNA hybrid duplexes with uniformly **2**'-deoxy-**2**'-**fluoro-modified oligonucleotides** did not support HeLa RNase H activity; however, incorporation of the **modifications** into "chimeric" **oligonucleotides** has been shown to activate mammalian RNase H. "Uniformly" **modified 2**'-deoxy-**2**'-**fluoro** phosphorothioate oligonucleotides afforded antisense molecules with (1) high binding affinity and selectivity for the RNA target and (2) stability toward nucleases.

L14 ANSWER 63 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 115:232781 CA
TITLE: Preparation of **2**'-**modified nuclease-resistant**

oligonucleotide

INVENTOR(S): Buhr, Chris A.; Matteucci, Mark
PATENT ASSIGNEE(S): Gilead Sciences, Inc., USA
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9106556	A1	19910516	WO 1990-US6090	19901024
W: AU, CA, JP, KR				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
CA 2071510	AA	19910425	CA 1990-2071510	19901024
AU 9067157	A1	19910531	AU 1990-67157	19901024
AU 658562	B2	19950427		
EP 497875	A1	19920812	EP 1990-916605	19901024
EP 497875	B1	20000322		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 05504552	T2	19930715	JP 1990-515636	19901024
EP 942000	A2	19990915	EP 1999-107747	19901024
EP 942000	A3	20000315		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AT 190981	E	20000415	AT 1990-916605	19901024
US 5466786	A	19951114	US 1994-240508	19940510
US 5466786	B1	19980407		
US 5792847	A	19980811	US 1995-467422	19950606
US 6476205	B1	20021105	US 1998-131647	19980810
US 2003036649	A1	20030220	US 2002-186058	20020627

PRIORITY APPLN. INFO.:

US 1989-425857	A	19891024
EP 1990-916605	A3	19901024
WO 1990-US6090	A	19901024
US 1994-240508	A1	19940510
US 1995-467422	A1	19950606
US 1998-131647	A1	19980810

OTHER SOURCE(S): MARPAT 115:232781
GI

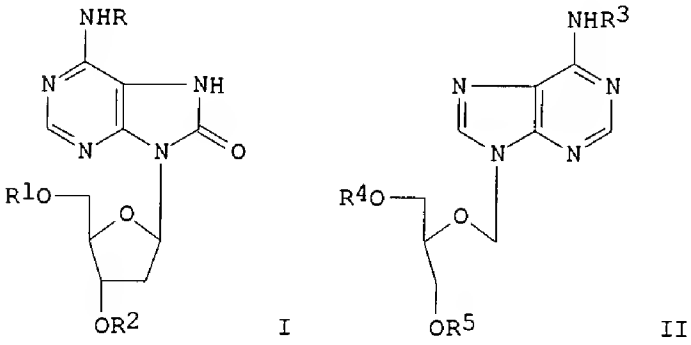
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB **2'-Modified oligonucleotide** I [B = purine or pyridimidine residue; R3,R4 = H, PO3-2, protecting group, hydroxyl linking group; n = 1-220; Z = linking group, e.g., P(O)O, P(O)S, P(O)NR, etc.; R = H, C16 **alkyl**; A = H, (protected) OH, XY; X = O, S, NR, CRR; Y = linker, drug residue, e.g., netropsin, anthramycin, C2-6 **alkyl**, (substituted) C6-20 aryl] were prepd. via **oligomerization** of monomers II [R3 = H, (PO3)m, protecting group, hydroxyl linking group; m = 1-3; all others defined above]. The **oligomers** are **nuclease-resistant** and useful as **nucleic acid** hybridization probes (no data). Thus, 2'-N-acetylamino-3',5'-O-diacetyluridine was deacylated by KCN and treated with 4,4'-dimethoxytrityl chloride to give 2'-N-acetylamino-5'-O-(4,4'-dimethoxytrityl)uridine which was added to a mixt. of 1,2,4-triazole, 4-methylmorpholine, and PCl3 in CH2Cl. The mixt. formed was poured into 1M aq. Et3NH+HCO3- to give monomer III. This can be converted to title **oligomers** by known methods. Title dimers are said to be **resistant** to **nuclease** from snake venom for >140 min.

L14 ANSWER 64 OF 67 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 117:49168 CA
TITLE: Preparation of **modified oligodeoxynucleotides** having restriction enzyme recognition sequences and DNA containing them
INVENTOR(S): Takaku, Hiroshi; Ichikawa, Takashi; Komatsu, Hiroshi
PATENT ASSIGNEE(S): Tosoh Corp., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 03236396	A2	19911022	JP 1990-30432	19900210

PRIORITY APPLN. INFO.: JP 1990-30432 19900210
GI



AB **Modified oligodeoxynucleotides** contg. **2** '-deoxy-7,8-dihydro-8-oxoadenosine (I; R-R2 = H) (AOH) or 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]adenine (acycloadenosine) (II; R3-R5 = H) (acA), and DNA contg. them are prepd. Preferred **oligodeoxynucleotides** are d(GGXX1TTCC) (III) and d(GXX1TTC) (X = AOH, X1 = A; X = A, X1 = AOH; X = acA, X1 = A; or (X = A, X1 = acA). The restriction enzyme is preferably EcoRI. These **modified oligodeoxynucleotides** show high **nuclease resistance** and are useful as restriction enzyme inhibitors and ligands for purifn. of restriction enzymes by affinity chromatog. Introduction of the **modified oligodeoxynucleotides** to DNA prevents the cleavage of the DNA by the restriction enzyme, which broadens the choice of enzymes used in recombinant DNA tech. Thus, tritylation of I (R = Ac, R1 = R2 = H) with 4,4'-dimethoxytrityl chloride in pyridine and esterification of the resulting I (R = Ac, R1 = 4',4-dimethoxytrityl, R2 = H) with [(F3C)2CHO]3P in the presence of pyridine in CH2Cl2 followed by hydrolysis in 1M Et3NHHCO3 buffer (pH 7.6) gave I [R = Ac, R1 = 4',4-dimethoxytrityl, R2 = P(O)HOH] which was used to prep. III (X = AOH, X1 = A) and III (X1 = A, X1 = AOH) by the manual solid phase synthesis. Similarly II [R3 = Bz, R4 = 4',4-dimethoxytrityl, R5 = P(O)HOH] was prepd. and was used to prep. III (X = acA, X1 = A) and III (X = A, X1 = acA). III were not hydrolyzed by EcoRI.

L14 ANSWER 65 OF 67 MEDLINE

ACCESSION NUMBER: 91334110 MEDLINE
DOCUMENT NUMBER: 91334110 PubMed ID: 1651474
TITLE: Synthesis and physicochemical properties of **oligonucleotides** built with either alpha-L or beta-L nucleotides units and covalently linked to an acridine derivative.
AUTHOR: Asseline U; Hau J F; Czernecki S; Le Diguarher T; Perlat M C; Valery J M; Thuong N T
CORPORATE SOURCE: Centre de Biophysique Moleculaire, CNRS, Orleans, France.
SOURCE: NUCLEIC ACIDS RESEARCH, (1991 Aug 11) 19 (15) 4067-74. Journal code: 0411011. ISSN: 0305-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199109
ENTRY DATE: Entered STN: 19911006
Last Updated on STN: 19911006
Entered Medline: 19910918

AB **Modified** deoxynucleosides **2**'-deoxy-beta-L-uridine, beta-L-thymidine, alpha-L-thymidine, 2'-deoxy-beta-L-adenosine and 2'-deoxy-alpha-L-adenosine were synthesized and assembled as homooligomers, respectively: octa-beta-L-deoxyuridylates, octa beta-L and alpha-L-thymidylates and tetra beta-L and alpha-L-deoxyadenylates. These unnatural **oligomers** were then substituted with an acridine derivative. The binding studies of these **modified oligonucleotides** with D-ribo- and D-deoxyribopolynucleotides were carried out by absorption spectroscopy. While beta-L-d(Up)8m5Acr, beta-L-(Tp)8m5Acr, alpha-L-(Tp)8m5Acr did not interact with poly(rA) and poly(dA), beta-L-d(Ap)4m5Acr and alpha-L-d(Ap)4m5Acr did form double and triple helices with poly(rU) and poly(dT), respectively. Their stability towards nuclease digestion was studied through comparison with that of octa-beta-D-thymidylate and tetra beta-D-deoxyadenylate covalently linked to an acridine derivative. One endonuclease (nuclease P1 from Penicillium citrinum) and two exonucleases (a 3'-exonuclease from Crotalus durissus venom and a 5'-exonuclease extracted from calf thymus) were employed. beta-L- and alpha-L-**oligomers** demonstrate a high **resistance** toward **nuclease** digestion.

L14 ANSWER 66 OF 67 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1990:112998 BIOSIS
DOCUMENT NUMBER: BA89:62489
TITLE: NUCLEOTIDES PART XXXI. **MODIFIED OLIGOMERIC 2'-5' OLIGOADENYLATE** ANALOGUES SYNTHESIS OF 2'-5' OLIGONUCLEOTIDES WITH 9-3' **AZIDO**-3'-DEOXY-BETA-D-XYLOFURANOSYLADENINE AND 9-3' **AMINO**-3'-DEOXY-BETA-D-XYLOFURANOSYLADENINE AS MODIFIED NUCLEOSIDES.
AUTHOR(S): HERDEWIJN P; CHARUBALA R; PFLEIDERER W
CORPORATE SOURCE: FAK. CHEM., UNIV. KONSTANZ, UNIVERSITAETSSTR. 10, D-7750 KONSTANZ.
SOURCE: HELV CHIM ACTA, (1989) 72 (8), 1729-1738. CODEN: HCACAV. ISSN: 0018-019X.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB A series of new 2'-5' oligonucleotides carrying the 9-(3'-**azido**-3'-deoxy-.beta.-D-xylofuranosyl)adenine moiety as a building block has been synthesized via the phosphotriester method. The use of the 2-(4-nitrophenyl)ethyl (npe) and 2-(4-nitrophenyl)ethoxycarbonyl (npeoc) blocking groups for phosphate, **amino**, and hydroxy protection guaranteed straightforward syntheses in high yields and easy deblocking to form the 2'-5' trimers 21, 22, and 25 and the tetramer 23. Catalytic

reduction of the **azido** groups in [9-(3'-**azido**
-3'-deoxy-.beta.-D-xylofuranosyl)adenin]-2'-yl-[2'-(Op-ammonio) .fwdarw.
5']-[9-(3'-**azido**-3'-deoxy-.beta.-D-xylofuranosyl)adenin]-2'-yl-
[2'-Op-ammonio) .fwdarw. 5']-9-(3'-**azido**-3'-deoxy-.beta.-D-
xylofuranosyl)adenine (21) led to the corresponding 9-(3'-**amino**
-3'deoxy-.beta.-D-xylofuranosyl)-adenine 2'-5' trimer 26 in which the two
internucleotidic linkages are formally neutralized by intramolecular
betaine formation.

L14 ANSWER 67 OF 67 MEDLINE
ACCESSION NUMBER: 77087725 MEDLINE
DOCUMENT NUMBER: 77087725 PubMed ID: 827308
TITLE: Location of accessible bases in Escherichia coli formylmethionine transfer RNA as determined by chemical **modification**.
AUTHOR: Schulman L H; Pelka H
SOURCE: BIOCHEMISTRY, (1976 Dec 28) 15 (26) 5769-75.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197703
ENTRY DATE: Entered STN: 19900313
Last Updated on STN: 19970203
Entered Medline: 19770331

AB Chemical **modification** of Escherichia coli tRNAfMet with 1 M chloroacetaldehyde, pH 5.5-6.0 at 25 degrees C, has been found to result in alteration of six cytidine and five adenosine residues in the molecule. The **modified** cytidine residues are the same as those previously found to be reactive with sodium bisulfite at pH 6.0. The accessible adenosine residues are A36 in the anticodon, A58 in the T psi C loop, and A73, A74, and A77 in the 3; terminal sequence. No **modification** of adenosine residues in the dihydrouridine or variable loops or of adenosine residues on the 3' side of the anticodon loop could be detected. Treatment of fMet-tRNAfMet with chloracetaldehyde gave the same pattern of midofication as was observed with deacylated tRNAfMet. Chemical **modification** of E. coli tRNAfMet with **2** sodium bisulfite, pH 7.0 at 25 degrees C, resulted in selective **modification** of exposed uridine residues in the tRNA. Only three sites were found to be reactive: U18 in the dihydrouridine loop, U37 in the anticodon, and U48 in the variable loop. The overall pattern of chemical **modification** of tRNAfMet is very similar to that found by others for yeast tRNAPhe, supporting the idea that many of the tertiary interactions in the two tRNAs are the same. The adenosine residue at position 58 in the center of the T psi C loop of the initiator tRNA shows unusual reactivity, however, being **modified** by chloroacetaldehyde at the same rate as the 3' terminal adenosine residue. This result is in sharp contrast to the uniform **resistance** of **nucleotides** in the T psi C loop of yeast tRNAPhe to chemical **modification**.

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FULL ESTIMATED COST	268.02	268.65

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